RELAPSE-PREVENTIVE EFFORTS TO SUSTAIN LONG-TERM REMISSION IN DEPRESSIVE DISORDERS

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Abstract

The present thesis focuses on relapse-preventive efforts during psychotherapy to sustain long-term remission in depressed individuals being at high risk for relapse and recurrence. Relapse prevention in the context of this thesis includes providing of continuation and maintenance treatments as well as enhancing transfer of therapy achievements into time after termination of therapy. The first study determined current evidence on psychological and pharmacological continuation and maintenance treatments in individuals suffering from persistent depressive disorder within a systematic review and meta-analysis, showing that only a few studies are available in this field. Therefore, we piloted a telephone-based continuation therapy for high-risk depressed individuals to assess feasibility and acceptance of this low-intensity intervention within the second study, applying an exploratory mixed-methods approach combining qualitative and quantitative data to obtain in-depth understanding of the intervention's new components. If several preconditions including low level of depressive symptoms and effective coping strategies are ensured, the intervention is considered feasible and accepted. The third study explored relapse-preventive efforts during psychotherapy, which focus on the implementation of strategies into patient's daily routines. For this purpose, we developed an observer-based rating instrument called the KERI-D (Coding System to Assess Interventions of Relapse Prevention in Depression), which showed sufficient inter-rater and retest reliabilities, and moreover, first evidence of content validity was demonstrated.

Zusammenfassung

Diese Dissertation fokussiert auf psychotherapeutische Behandlungsmöglichkeiten, die darauf abzielen rückfallgefährdeten Depressionspatienten auf lange Sicht ein Leben in Remission zu ermöglichen. Rückfallprophylaxe in diesem Kontext schliesst sowohl das Bereitstellen und die Inanspruchnahme von Erhaltungstherapien und Rezidivprophylaxe ein, als auch den verbesserten Transfer vom in der Therapie Erlernten in den (behandlungsfreien) Alltag. Die erste Studie schätzt in Form eines systematischen Reviews und einer Meta-Analyse die aktuelle Befundlage zu psychologischen und pharmakologischen Erhaltungstherapien und Rezidivprophylaxe bei Personen mit persistierender Depression ein, wobei nur wenige Studien in diesem Bereich existieren. Daher wurde innerhalb der zweiten Studie eine telefongestützte Erhaltungstherapie für Depressionspatienten mit erhöhtem Rückfallrisiko pilotiert. Die Akzeptanz und Machbarkeit der neuen Komponenten dieser Behandlung wurde, basierend auf der Kombination von qualitativen und quantitativen Daten, durch beteiligte Patienten und Therapeuten eingeschätzt. Die Intervention scheint durchführbar und akzeptiert zu sein, wenn gewisse Rahmenbedingungen wie tiefer Symptomstatus und wirkungsvolle Copingstrategien sichergestellt werden. Die dritte Studie hat rückfallprophylaktische Behandlungsbausteine untersucht, die auf die Implementierung des in der Psychotherapie Erlernten in den Alltag des Patienten fokussieren. Dazu haben wir ein Ratinginstrument entwickelt (KERI-D: **K**odierbogen zur **E**rfassung **R**ückfallprophylaktischer **I**nterventionen bei **D**epression), welches zufriedenstellende psychometrische Eigenschaften zeigt.

“My recovery has been an evolution, not a sudden miracle”

Patty Duke

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1 Introduction

Depressive disorders are associated with a high risk of relapse and recurrence [1], especially if kept untreated [2]. Reasons for the recurrent and persistent nature of depression are focus of scientific inquiry for decades, including factors associated with the patient (e.g., genetic vulnerability, cognitions) [1] and factors located within the health care system (e.g., availability and application of evidence-based treatments) [3]. Several interventions for depression treatment (e.g., antidepressant medication, psychotherapy, and their combination) were developed and evaluated for their feasibility and effectiveness within large and well conducted trials to date [4]. However, most of these studies address episodic forms of depression during the acute treatment phase. Despite promising short-term results of such acute phase interventions we are confronted with the problem that studies also show that 30-50% of depressive disorders are turning chronic during the course of an individual's lifetime [5]. This allows for discussion whether or not the current treatment concepts can prevent relapse and recurrence in the long-term.

Whilst providing interventions during the acute treatment phase is currently the way of care which is mostly provided, long-term continuation and maintenance treatment might be required for individuals who are at high risk for relapse or recurrence of symptoms [6]. Continuation treatments are provided to currently remitted patients or to patients who previously responded to treatment, and maintenance treatments are given only during recovery, which is defined as remission lasting longer than six months [7, 8]. Most studies to date investigate pharmacological long-term treatments assuming relapse preventive effects in high-risk individuals. At the same time, patients report on severe side-effects resulting in discontinuing antidepressant medication without the doctor's agreement, which in turn increases likelihood of relapse [9]. Psychological long-term interventions can meet this condition by focusing on enduring behavioral change which might be less associated with

adverse events [10]. Moreover, as individuals with recurrent or persistent depression commonly take antidepressant medication, psychotherapy might support relevance and continuous intake of drugs.

As outlined above, several attempts to meet the recurrent and persistent character of depression had been made in the past, mostly focusing on short-term acute phase treatments and pharmacological interventions. With respect to high relapse and recurrence rates, this thesis will address relapse-preventive efforts of treatments for depressive disorders to sustain remission and recovery in the long-term. All three studies presented in this thesis take the potential recurrent or persistent character of depression into account by investigating the form and impact of continuation and maintenance treatments in high-risk individuals. Moreover, relapse-preventive elements implemented during psychotherapy, which encourage the patient to transfer therapy achievements into time after termination of treatment or to long-term treatments will be considered.

Core concepts of relapse prevention and current evidence on according treatment options in several forms of depressive disorder are presented in chapter 2. Specific research questions underlying the aim of the three studies of this thesis will be presented in chapter 3, followed by displaying each of the studies in chapter 4. Study 1 illustrates the current evidence on the general effectiveness of continuation and maintenance treatments for individuals suffering from persistent depressive disorder by means of a systematic review and meta-analysis. Study 2 addresses the question if a telephone-based continuation psychotherapy is feasible and accepted by therapists and their patients suffering from recurrent or persistent depression. Finally, study 3 focuses on relapse-preventive efforts initiated by therapists during psychotherapy, which might contribute to the relapse-preventive effect of psychotherapy in (several) depressive disorders.

2 Theoretical background

2.1 Depression is a recurrent and persistent disorder

Depressive disorders are associated with a high risk of relapse and recurrence [1] especially if kept untreated [2]. Moreover, relapse and recurrence rates remain high even with evidence-based treatments [11, 12]. Studies indicate that approximately 50% of individuals who recovered from an initial depressive episode will experience one or more further episodes in the future, and that such recurrent episodes will usually begin within five years after the initial episode had occurred [13, 14]. Moreover, it is estimated that individuals with a history of depressive disorder will experience between five and nine episodes in their lifetime [15, 16]. Regarding persistent forms of depression, the mean duration of illness is between 17 and 30 years [17, 18], and lifetime prevalence is estimated to range from 3% to 6% in the Western world [19–21]. Thus, research focusing on the prevention of relapse and recurrence of depression was identified as a top priority [22].

The one big question researchers have been interested in for decades is "Why do individuals relapse?", and obviously, there are several different factors discussed to be accountable for the recurrent or persistent character of this illness. The most pessimistic explanation strikes the illness itself and states that depressive disorders are recurrent or persistent by nature [1]. This hypothesis assumes that affected individuals may have an underlying (genetic) vulnerability, and that those individuals with high vulnerability might be predisposed to experience recurrent depressive episodes. Greater family history of psychopathology, more comorbidities and more severe initial episodes of depression might also reflect a genetic vulnerability in individuals affected by recurrent and chronic forms of depression besides environmental influences [23]. In this regard, the diagnosis of a "Depressive Personality Disorder" (DPD) has been discussed for many years to account for persistent depressive symptoms in terms of a rather stable trait, with an early onset and

recurrent or chronic course [24]. Due to a conceptual overlap with the already established diagnosis of dysthymia, DPD was not considered a distinct diagnosis in the Diagnostic and Statistical Manual of Mental Disorders [13, 25], although there is open discussion if DPD could better account for underlying depressive cognitive and intrapsychic symptoms than dysthymia [26]. However, with the presence of permanent depressive personality traits it might be assumed that treatment would be likely to not be beneficial as these attitudes are part of a subject's character and therefore unchangeable.

Other explanations for the recurrent or persistent character of depressive disorders are mostly located within the health care system [3]. Studies show that subjects affected by depressive symptoms seek professional medical help with a delay of eight years on average after the first occurrence of their problems [27]. It is assumed that affected people wait for such a long time despite their distress due to fear of stigmatization and lack of knowledge about depression and its treatment options [28]. As a consequence, depressive symptoms might persist over the years and likelihood of successful later treatment might diminish.

Even once subjects enter the health care system it is still not guaranteed that they receive adequate treatment, and on several steps within the system problems might occur. Most patients usually seek help first from their general practitioner (GP), and studies show that GPs often fail to detect depressive symptoms accurately [29], considering more often a somatic cause for symptoms by neglecting possible mental health problems [30]. If depression is diagnosed correctly, GPs tend to increasingly prescribe antidepressant medication [31] although clinical guidelines contain distinct treatment options depending on severity of current depressive episode and development and kind of current and past symptomatology [6]. Moreover, most patients would prefer to receive psychotherapy to solve the cause of their depression, while antidepressants are regarded to be addictive [32].

One relevant issue in this context is lack of professional networking, which likely contributes to providing antidepressant medication as first choice treatment. Studies show that

physicians are rarely referring their patients to mental health professionals (psychotherapists or psychiatrists) because they often have limited knowledge regarding mental health providers located nearby and the range of effective treatments [33]. All of these reasons for lacking adequate and timely treatment might contribute to the likelihood that depression is turning recurrent or chronic over time.

However, even if a patient actually is referred to a mental health professional in time, it is still not guaranteed that he will receive adequate treatment, considering that only a marginal amount of psychotherapists ground their treatments on evidence-based techniques recommended by clinical guidelines [34]. Finally, assuming a patient does receive state of the art treatment – can we know for sure that this treatment will help the patient to recover from depression *in the long-term*? In research and clinical practice we are currently confronted with the problem that we are considered to have effective evidence-based treatments, but at the same time studies show that 30-50% of depressive disorders are turning persistent during the course of an individual's lifetime [5]. This allows for discussion whether or not the current treatment concepts can prevent relapse and recurrence in the long-term.

This thesis tries to contribute to the discussion whether or not we have adequate treatment concepts for depressive disorders in order to sustain remission in the long-term, and if and in what way there is room for improvement of these treatments. Recurrent and persistently depressed individuals in particular are at high risk for further relapse and recurrence, which is why the major part of this thesis will focus on this patient population.

2.1.1 Recurrent and persistent forms for depression

The majority of individuals with depression will experience more than one lifetime major depressive episode [5]. Long-term depression can take several courses over time, with individuals showing distinct episodes with few or no symptoms between episodes, and

individuals rarely or never remitting from episodes at all [13]. In research literature a clear distinction between these two forms is made.

Recurrent depression, referred to as "recurrent depression with full inter-episode recovery" in the diagnostic classification system DSM-5 [13], is characterized by more than one episode of major depressive disorder and full remission between episodes. Although individuals experience several episodes over their lifetime, they also experience months or even years without any depressive symptoms, so that this form of depression is *not* considered to be persistent.

By contrast, *persistent forms of depression* are newly referred to as "persistent depressive disorder" (PDD) in the DSM-5 [13], and contain four diagnostic subgroups characterized by an illness duration of at least two years: (1) dysthymia, (2) chronic major depression, (3) recurrent major depression with incomplete remission between episodes, and (4) double depression [35]. Dysthymia is defined as a condition with mild depressive symptoms persisting for at least two years. Chronic major depression refers to a more severe condition that meets full criteria for a major depressive episode continuously for a minimum of two years. Individuals who have recovered to the point at which they no longer meet full criteria for a major depressive episode but continue to experience significant symptoms for at least two years are referred to as suffering from recurrent major depression with incomplete remission between episodes. The superimposition of a major depressive episode on antecedent dysthymia is referred to as double depression [20].

Both PDD and recurrent depression are associated with severe impairments as for instance increased loss of physical wellbeing, more frequent suicide attempts, less social, psychological and emotional functioning, more hospitalizations, and longer treatment duration compared to non-persistent or non-recurrent forms of depression [1, 17, 36, 37]. Those individuals are therefore in urgent need for treatments that focus on diminishing these consequences but also on preventing further relapses or recurrences in the future.

2.1.2 Treatment phases

One opportunity to minimize likelihood of relapse and recurrence in depressive disorders is to provide relapse-preventive treatment. Considering an entire treatment period there are three treatment phases conceivable [38]: acute phase, continuation phase and maintenance phase treatments (see figure 1). Interventions *during the acute phase* aim to reduce depressive symptoms and to maintain the individual's functional level - also beyond termination of acute treatment. Following response to acute treatment, long-term continuation and maintenance treatment might be required for individuals who are at high risk for relapse or recurrence of symptoms [6]. Whilst continuation treatments are provided to currently remitted patients or to patients who previously responded to treatment, maintenance treatments are given only during recovery, which is defined as remission lasting longer than six months [7, 8]. All three types of interventions intend to prevent patients from experiencing relapse (return of depressive symptoms before full remission has been achieved) or recurrence (appearance of another episode of depression after full remission) [8].

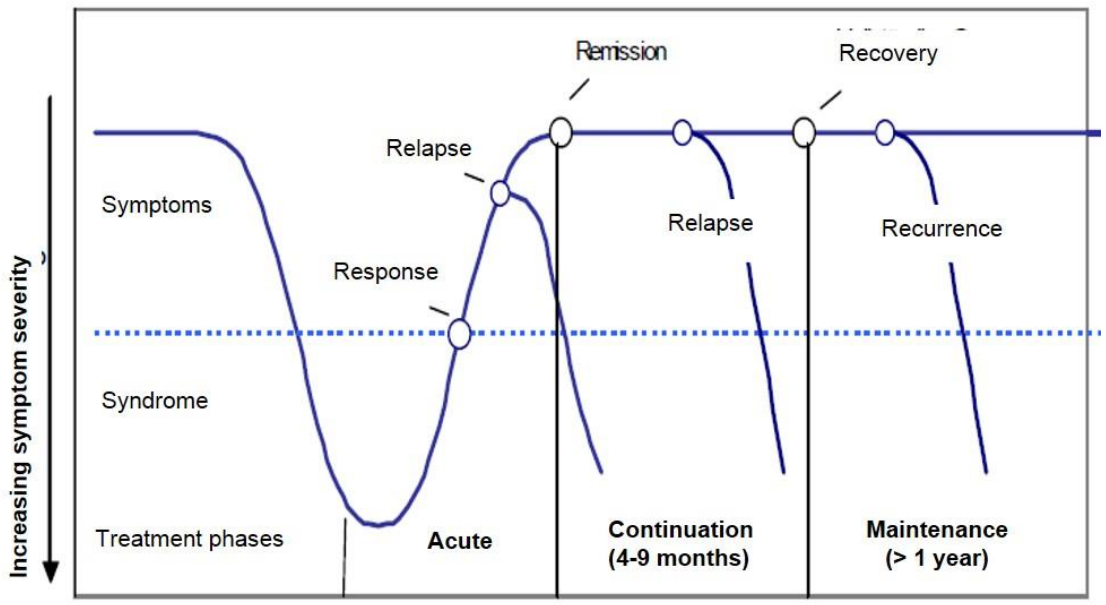

Figure 1. Treatment phases depending on response and remission status of the patient. Retrieved and adapted from DGPPN et al. (2009).

With regard to pharmacological treatment, clinical guidelines recommend to continue ADM with the same dose received during acute treatment, considering a tapering down of ADM by the end of continuation and maintenance treatment phase [6]. By contrast, psychotherapeutic continuation and maintenance treatments are not considered a simple extension of acute therapy [39], but rather contain the generalization of skills a patient acquired during acute treatment to daily routine situations. This usually manifests in a less frequent therapeutic setting, i.e., longer intervals between sessions are considered meaningful.

As relapse-preventive efforts can be located throughout the entire treatment period, this thesis will give insight into all three treatment phases described above, predominantly focusing on psychotherapeutic efforts to prevent relapse and recurrence. The next chapter will give an overview on current evidence on pharmacological and psychological treatment options in major depressive disorder (MDD) and PDD, highlighting the relevance and need for further research of psychological treatments.

2.2 Effectiveness of pharmacological and psychological treatments for major depressive disorder

2.2.1 Acute phase treatments for MDD

Extensive research was done in this field, mostly in so called "relapse-preventive trials". These trials provide patients with a specific amount of treatment, usually between 6 and 12 weeks [6], intending to reduce depressive symptoms by the end of the intervention, and to sustain response or remission also beyond terminating acute phase treatment. Studies indicate that *pharmacological treatment* is effective in reducing depressive symptoms compared to placebo [40], and that, on average, pharmacological agents do not substantially differ in their effectiveness [41]. Studies also show that pharmacological treatment is only effective as long as patients take antidepressant medication (ADM), but that depressive

symptoms re-emerge after discontinuation of ADM [42]. Moreover, receiving ADM is associated with experiencing adverse events, mostly in the form of side effects (e.g., headache, insomnia), which often lead the patient to stop taking the drugs [9].

With regard to *psychological treatment*, acute phase psychotherapy is proven to be effective in reducing symptoms even beyond termination of acute phase psychotherapy, with most studies investigating the effects of cognitive therapy (CT) or cognitive-behavioral therapies (CBT) [12, 43]. In their meta-analysis, Vittengl and colleagues [12] found acute phase CBT superior to acute phase ADM, showing that 39% of participants receiving CBT had a relapse or recurrence compared to 61% of participants receiving ADM over a mean of 68 weeks after terminating treatment.

Additionally, the authors were interested in possible *add-on effects of either of these treatments*. The combination of ADM and CBT resulted in significantly less relapses or recurrences compared to ADM alone within 56 weeks after terminating treatment. By contrast, the combination of ADM and CBT did not differ from CBT alone regarding relapse and recurrence during follow-up, but only three studies contributed data, limiting conclusions of this comparison [12]. In recent years interventions also target ‘third wave' cognitive and behavioral therapies which include strategies addressing mindfulness exercises and acceptance of unwanted thoughts and feelings. A recent meta-analysis found that these therapies were superior to treatment as usual regarding clinical response rates at end of intervention [44]. The authors noted that this result is based on a small amount of included studies (n = 4), with limitations in methodological quality, and lack of follow-up data.

2.2.2 Continuation and maintenance phase treatments in MDD

Clinical guidelines recommend to continue treatment to maintain remission and recovery in the long-term [6, 45]. These guidelines differ in specifying the duration of

continuation and maintenance treatments (between four months and two years), but agree that the treatment, which proved to be effective during acute treatment, should be continued and maintained in the following phases, and that patient's preference on type of treatment should be taken into account. Studies indicate that *pharmacological continuation and maintenance treatments* are effective in reducing depressive symptoms compared to placebo [42, 46], indicating no substantial differences between pharmacological agents.

With regard to *psychological continuation and maintenance treatments*, CBT did not differ from other active treatments (e.g., ADM) by end of continuation/maintenance treatment, but showed better outcomes (i.e., fewer relapses and recurrences) compared to ADM during 114 weeks of follow-up on average [12]. Moreover, compared to non-active controls (e.g., assessment only), participants receiving continued or maintained CBT had fewer relapses and recurrences by the end of intervention and at follow-up. In recent years, the Mindfulness-Based Cognitive Therapy (MBCT) obtained attention in reducing relapse and recurrence in depressed individuals currently in partial or full remission [47, 48], teaching the patient to deal with negative feelings and thoughts *as a part of their lives* through becoming aware of negative cognitive patterns. The meta-analysis of Piet and Hougaard [47] showed that for individuals with recurrent depression (with full inter-episode recovery) MBCT significantly reduced risk of relapse and recurrence compared to treatment as usual or placebo control, if participants had experienced at least three or more depressive episodes. By contrast, MBCT did not differ from continued/maintained ADM based on two studies. Although MBCT seems to be a promising approach in preventing relapse and recurrence, there is open discussion if MBCT is actually a continuation treatment program. MBCT studies include remitted patients but without requiring the patients to have received an acute phase treatment beforehand, so it remains unclear how patients remitted. Also, MBCT programs offer eight sessions of group therapy providing the main concept of MBCT to participants, which means that participants actually learn new strategies and techniques. As continuation

and maintenance interventions intend to maintain the already gained during acute treatment, MBCT programs might be considered a different approach.

The body of research indicates that acute, continued and maintained interventions are effective in individuals with major depressive disorder, including individuals with recurrent depression with full inter-episode recovery. Still, it remains challenging to completely understand the mechanisms of relapse and recurrence prevention in the short- and long-term [49].

2.2.3 Mechanisms of change

Whilst pharmacological treatments are considered to mainly target symptoms on a physiological level, psychological treatments intend to target origin and maintenance of depression by challenging attitudes and changing behavior. The exact therapeutic mechanisms of *pharmacological treatments* are still critically discussed [50]. However, most ADMs seem to increase the concentration of monoamine neurotransmitters in the synaptic cleft [51]. Depending on the type of active ingredient, ADMs can have mood-enhancing, anxiolytic or sedative effects and are able to increase or decrease inner drive.

Regarding *psychological treatments*, process-outcome researchers are interested in how therapy works, i.e., finding specific mechanisms during psychotherapy potentially underlying patients symptom change [52]. Recently, Lemmens and colleagues [53] reviewed 35 studies identifying psychological mediators in psychotherapy for depression. Considering only high quality studies (n = 17), behavioral concept of CBT and worry were the most often found significant mediators regarding outcome change (depression severity), followed by dysfunctional attitudes, negative (automatic) thoughts, mindfulness skills, attributional style, rumination, and therapeutic alliance. Most of these found mechanisms are theorized processes of therapies based on cognitive or cognitive-behavioral concepts. This was expected as 21/35

studies addressed CBT interventions. The authors of this review were careful with final conclusions due to unsatisfactory methodological quality of included studies. For instance, only two studies could accurately assess the temporal association between change in the mediator and change in outcome on a session-by-session basis, and none of the studies manipulated the mediator experimentally to test for causal processes [53]. Next to methodological recommendations the authors conclude that there is a need for improving theory behind processes of change followed by developing valid mediator measures using multiple sources of information (e.g., self-report, independent raters, behavioral measures).

This thesis will have a closer look on therapeutic processes, which might be involved in patients´ symptom change. This is addressed by the development of a new observer-based instrument to assess relapse-preventive efforts during psychotherapy (study 3), aiming to contribute to sustained remission in the long-term.

2.3 Effectiveness of pharmacological and psychological treatments for persistent depressive disorder (PDD)

The previous chapter demonstrated that there are indeed effective acute and continuation/maintenance treatments (ADMs, psychotherapy) for individuals suffering from major depressive disorder or recurrent depressive disorder (with full inter-episode recovery). As these patients experience remission and recovery, treatment might be different from that provided to individuals who suffer from PDD, as these patients experience constant depressive symptoms for at least two years. This chapter will point out current evidence on treatment options in PDD.

2.3.1 Acute phase treatments for PDD

Meta-analyses agree that *pharmacological treatments* show better outcomes (response/remission rates) compared to psychotherapy in purely dysthymic patients [43, 54–56], and they found selective-serotonin-reuptake-inhibitors (SSRIs) to be specifically effective in dysthymic patients. Generally, ADM is superior to placebo regarding response and remission rates [56, 57], and especially the drugs fluoxetine, paroxetine, sertraline, moclobemide, impipramine, and amisulpride are considered efficacious and acceptable [56]. One meta-analysis found no differences regarding response rates between SSRIs and tricyclic antidepressants (TCAs), but SSRIs were more acceptable in terms of dropout rates compared to TCAs [57].

Evidence regarding the effectiveness of *psychological treatments or combined treatment* of ADMs and psychotherapy is rather inconclusive, especially due to marked heterogeneity between trials in terms of kind of psychotherapy and specific combination with an antidepressant agent and diagnostic subgroup. Two kinds of psychotherapy are mostly researched in PDD: interpersonal therapy (IPT) and the Behavioral Analysis System of Psychotherapy (CBASP). While IPT is mostly provided for dysthymic patients, CBAPS is mostly provided for patients with a chronic major depressive disorder in studies [56]. Two meta-analyses found indicators that combined treatment of ADM and psychotherapy might be superior to a stand-alone treatment in regard to response/remission rate [54, 56]. By contrast, von Wolff and colleagues [58] found combined treatment equally effective as ADM alone, although participants receiving combined treatment reported better quality of life at end of intervention compared to participants receiving ADM alone.

Besides proposed benefits of acute treatment in PDD, pharmacological and psychological interventions might also be associated with adverse events (side effects, behavioral changes, hospitalization). If two treatments seem equally effective, the choice for

one treatment over the other might be based on suggested differences regarding adverse events. A recent meta-analysis identified 60 studies addressing pharmacological, psychological and combined treatments in PDD and concluded that adverse events were insufficiently considered in evaluated studies [59]. Whilst pharmacological and combined studies mostly reported adverse events, the majority of psychotherapeutic studies did not. Generally, psychotherapeutic studies often fail to report adverse events [60, 61], which should be considered when comparing outcomes of ADMs and psychotherapy studies.

Research clearly indicates that pharmacological treatment is effective and accepted in PDD, and it might be an advantage to provide additional psychotherapy. Yet, given the high rates of relapse and recurrences following response to acute treatment, long-term continuation and maintenance therapy are of great importance [49].

2.3.2 Continuation and maintenance phase treatments for PDD

Although the vast majority of evidence addresses acute treatments for PDD, some studies have been conducted to address the effectiveness of continuation and maintenance treatments [62–70]. The majority of studies investigating continuation and maintenance treatments in PDD focus on long-term ADM, include different pharmacological agents and show their superiority compared to placebo regarding relapse and recurrence rates [62–64, 66, 71].

CBASP [72] is a program especially developed for *psychotherapeutic treatment* of PDD and has been subject of scientific inquiry in recent years. The program itself combines techniques from IPT and CBT programs, focusing on early traumatic events and relationships, which might have let to specific behaviors such as interpersonal avoidance. Most results on the effectiveness of CBASP are based on one study involving 681 outpatients receiving either nefazodone (ADM) or CBASP (psychotherapy) or both during the acute [73] and continuation phase [67]. This study also involved a maintenance phase in which patients

received either ADM or placebo [62], or either CBASP or assessment only [65]. The continuation phase study found no differences between the three treatment arms, i.e., CBASP alone, nefazodone alone, and combination of CBASP and nefazodone were equally effective [67]. By contrast, participants receiving nefazodone during 52 weeks of maintenance treatment showed fewer relapses and recurrences compared to participants receiving placebo [62], and also, receiving CBASP during this treatment phase was associated with fewer relapses and recurrences compared to assessment only [65]. This multi-center study attracted much attention as it found promising effects of long-term psychotherapy that were comparable to the effects of stand-alone pharmacological treatment, which was the state of the art treatment until then. However, this study was also criticized because of a missing untreated control group and use of an ADM (nefazodone) which was withdrawn from the market in 2004 in some countries due to the rare incidence of hepatoxicity [74].

Despite the relevance of providing continuation and maintenance treatments in individuals being at high risk of relapse and recurrence [6], only a few studies address those treatment phases, and these studies differ in their methods and found results. Thus, we conducted a systematic review and meta-analysis on the effectiveness of pharmacological and psychological continuation and maintenance treatments in PDD patients. This topic is addressed by study 1 of this thesis, and was conducted in cooperation with the Cochrane Collaboration. This organization is a global independent network of researchers and professionals, aiming to provide the best and most current evidence on different kinds of treatments. Cochrane holds a comprehensive database of systematic reviews[1], and monitors the whole developmental process to improve quality of systematic reviews published in their database.

[1] http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/

2.4 Enhancing relapse-preventive efforts throughout and beyond therapy

2.4.1 Methods for assessing and evaluating relapse-preventive efforts

As outlined in the previous chapters, there is a vast amount of research on relapse-preventive effects of different kinds of treatments in different forms of depressive disorder. The majority of these studies focus on the general effect of acute, continuation or maintenance treatments following the question whether outcomes differ substantially between treatment arms and over time. Outcomes typically addressed in studies are rates of relapse/recurrence, level of depressive symptoms or dropout, often measured within a pre-post design [53]. Usually, studies in this field of *outcome research* do not assess by which means psychotherapy produces its effects [75]. Thus, researchers assume that such treatments generally help to minimize likelihood of relapse and recurrence, but without assessing the specific mechanisms potentially underlying symptom change in patients. *Process-outcome studies* measure different kinds of processes of both the therapist (e.g., specific techniques) and the patient (e.g., motivation) throughout therapy that might lead to patient change [76]. Studies try to investigate possible mediators that drive the effects of treatment, and that relapse prevention trials ideally need a session-by-session assessment to evaluate temporal changes [53].

To conduct such relapse prevention trials, usually a considerable number of therapists are involved, and in order to conclude afterwards that a specific treatment has been effective it is necessary for all therapists to provide the treatment in the same way. Otherwise, one cannot know whether the individual therapist and his/her specific attitudes drive the main effects, or if the treatment concept and sessions including strategies and exercises are responsible for the measured effects (very likely, both aspects including their interaction is the most realistic explanation). In psychotherapy research, this issue is addressed by *treatment integrity*, which is defined as both adherence (to a treatment concept or manual) and competence of a therapist

[77]. *Adherence* is defined as the degree to which a therapist provides interventions as determined in the treatment manual, whereas *competence* is defined as the extent to which a therapist implements such techniques in a skillful manner [77]. Researchers wonder whether level of treatment integrity might have an impact on intervention effectiveness [78], with the idea that better implementation of treatment might lead to better outcomes in patients, possibly minimizing relapse and recurrence in the long-term. However, a meta-analysis addressing this question found no significant associations between adherence/competence and treatment outcome, which the authors attributed to the variety of applied methods (rating instruments, number of rated sessions, etc.), or to little influence of therapists' adherence and competence on patients' symptom change [79].

Indeed, a variety of reliable and validated instruments assessing therapist's adherence and competence during psychotherapy are available. These instruments usually target the core aspects of a treatment concept. For instance, if a scale is intended to measure adherence to a CBT intervention, it will probably measure if and to what degree a therapist addresses recognition of cognitive errors or distancing oneself from beliefs during the sessions, as these aspects are considered main components of CBT interventions. The most influential adherence scale is the Collaborative Study Psychotherapy Rating Scale [CSPRS; 80], and the most influential competence scale is the validated and frequently applied Cognitive Therapy Scale [CTS; 81]. Both scales use an observer-based format, i.e., independent observers evaluate the therapist's behavior by watching videotaped therapy sessions and rating the occurrence and degree of specific components. Having trained observers evaluate therapists´ behavior is considered more objective than relying on therapists´ self-reports of the accuracy of delivering the treatment [82].

Available adherence and competence scales focus on *processes in-session* and *within the acute phase treatment period*, aiming to ensure accurate implementation of core treatment concepts to increase likelihood of good outcomes at the end of the intervention and during

follow-up, resulting in a relapse-preventive effect of treatment. Interestingly, established treatment manuals for acute psychotherapy in cognitive and interpersonal therapies (Ellis and Dryden, 1997; Hollon et al., 2002; Beck et al., 2010; Schramm and Berger, 2010; Hautzinger, 2013) include specific recommendations for relapse prevention techniques which exceed core concepts represented in adherence and competence scales. More specifically, elements that can be rehearsed in the final treatment phase include: early detection of depressive symptoms, anticipating critical situations and adequate coping skills, maintaining antidepressant activities, activating resources, reinforcing helpful cognitions, planning the future, summarizing the achievements of therapy, sensitizing the patient to potential relapses, and preparing transition from therapy to time after therapy termination. Although a variety of relapse prevention strategies seem to be recommended and commonly used in clinical practice, available scales assessing adherence and competence during psychotherapy do not fully cover the adequate implementation of relapse-prevention techniques beyond core treatment elements (e.g., central cognitions in CT).

The above mentioned scales target relapse prevention elements only to a marginal degree, i.e., through items such as 'Encouragement of self-monitoring' or 'relapse prevention,´ and these scales focus rather on the application of certain behaviors during treatment than on *preparing for their application after discontinuing treatment*. Especially for inpatients who receive acute treatment in hospital, strategies learned in this sheltered environment might not work properly in everyday life. We consider the transition of therapy gains between treatment phases as well as between therapy and life after termination of therapy a relevant aspect, which might be relapse-preventive next to core treatment concepts as explained above. Thus, we were aware of potential relapse preventive strategies that are currently not covered by existing instruments in research. Consequently, we intended to develop a measure to assess specific relapse prevention elements initiated by the therapist, which focus on the patient's implementation of strategies after termination of treatment, such

as anticipating critical situations and adequate coping skills or sensitizing the patient to potential relapses and recurrences in the long run. By this, we want to contribute to enhancing relapse-preventive efforts throughout and beyond psychotherapy, as described in study 3 of this thesis.

2.4.2 Challenges in providing and receiving continued treatment

Individuals who seek acute treatment are in urgent need for help and it is likely that providers will try to offer immediate treatment, and that health insurances will try to cover costs for this treatment. This is somewhat different regarding continuation treatments. First of all, continued treatment should be offered only to patients who responded to or remitted after a previous acute treatment [6, 45], which means patients are reporting a better health status. Thus, health insurances are probably less willing to cover the costs for treatment of an already remitted patient, and moreover, the patient might be eager to live without any therapeutic help at this point. Continuing treatment despite feeling well again might not be first choice of patients, which raises the question of how accepted continued treatments actually are. Acceptance of a treatment is usually reported by *dropout rates*, i.e., how many patients terminated therapy prematurely [83]. Generally, dropout rates tend to vary between 30% and 50% in studies addressing individual psychotherapy [83], and were found to be around 25% in a meta-analyses regarding individual and group CBT for unipolar depression in routine clinical practice [84]. In the same meta-analysis, authors reported that only 70% of investigators reported on the extent of dropout, and even if dropout was reported, intention-to-treat (ITT) analyses were rarely used compared to completer analyses [84].

Regarding acceptance of continuation treatments, we are especially interested in dropout rates between the acute and the continuation treatment - therefore studies that offer both treatment phases are required. The majority of such studies report dropout rates between

treatment phases, but also include non-responders to acute treatment into these dropout rates, keeping the reader uninformed on how many patients were actually eligible and have actively refused to enter continuation treatment for other reasons. One multi-center trial (of high methodological quality) on the comparative effectiveness of sertraline and imipramine in chronically depressed patients reported 24% dropout between the acute and continuation treatment phase, and a continuation phase completion rate of 86% [68]. Whilst reasons for dropout within one treatment phase are usually reported (e.g., 'intervention ineffective', 'adverse events'), reasons why patients are not willing to continue treatment are mostly unknown yet.

As already mentioned, low level of patients´ motivation due to stable current health status might be an explanation, but also that patients have to organize possible continuation treatment on their own because the health care system commonly does not provide distinct continuation programs or does not cover additional therapies beyond achieved remission [3]. The latter point addresses costs of continuation treatment, which request additional financial resources (compared to acute treatment only) but can increase treatment effectiveness, for instance in collaborative care programs in patients with PDD [85]. Moreover, it is assumed that the costs of lower workplace performance due to depression exceed the costs for treating the illness, which in turn can prevent the deterioration of patients´ workplace performance [86, 87].

There is not only the problem of funding evidence-based continuation treatments, but also in *facilitating access* to them. Despite available psychotherapeutic treatments, patients tend to make use of treatments delayed, or even never, also because of fear of stigmatization [33]. One study assessed perceived barriers to receiving psychological depression treatment, and found that higher scores on stigma, emotional concerns, misfit of therapy to needs, and time constraints predicted fewer reports of attending psychotherapy one year later [88]. Time constraints might be a relevant factor when discussing barriers to making use of continued

psychotherapy in patients being at high risk of relapse. For instance, the majority of patients suffering from PDD receive pharmacological treatment as it proved to be effective during acute, continuation and maintenance treatment phases (see previous chapters). Receiving a prescription of an antidepressant medication and taking pills each day might be "easier" for the patient in terms of expenditures (time, costs, etc.) compared to psychotherapy, although psychotherapy might have equal effects, a lower risk of side effects, and better long-term behavioral change compared to pharmacological treatments [10].

As low level of mood, interest and energy are key symptoms of depression, the above mentioned barriers have to be taken into account when conceptualizing continuation treatments. This raises the question of how we can increase the likelihood that patients enter and maintain continuation therapies, and by this increase likelihood of sustained remission.

2.4.3 Opportunities in providing and receiving continued treatment

To optimize patients' access to continuation treatment, several recommendations on system level can be made: better interdisciplinary cooperation between providers, establishing knowledge on evidence-based treatment options in providers, and developing low-intensity, easily accessible and flexible treatments [3]. *Stepped care programs* are considered to contribute to better access to treatment by a cooperative system in which providers can up- or downgrade level of treatment intensity depending on health status of the individual [89]. Multi-center trials in different countries investigated this complex system of treatment in depression, and they vary in results regarding effectiveness compared to care as usual [85, 90–92], leaving open discussion upon access, effectiveness and efficiency of stepped care programs [89].

Another opportunity to provide treatment to a wide range of patients, especially relapse-preventive treatments after termination of acute treatment, is seen in administering

low-intensity treatments, which are associated with fewer financial expenses due to less intense treatment and innovative delivery options [93]. Such treatments include less or even no direct therapeutic involvement compared to traditional (face-to-face) settings, for instance due to use of new technologies such as CBT provided over the internet or other mobile devices, and might involve highly qualified mental health professionals (e.g., psychotherapists) or non-professions (e.g., peer supporters). A systematic review regarding low-intensity psychological interventions to reduce relapse in depression found differing degrees of clinical effectiveness and cost-effectiveness of evaluated interventions [93]. Despite inconclusive results on average, the authors highlighted one study that implemented a relapse prevention intervention to improve adherence to ADM in recovered patients who were at high risk of relapse, providing two face-to-face and three telephone sessions as well as personalized mailings [94]. Although relapse/recurrence rates did not differ between participants in the program and those receiving care as usual over 12 months follow-up, adherence to ADM was greater compared to care as usual. The authors assumed that more intensive treatment might be required to reduce relapse and recurrence in high-risk patients [94]. Rodgers and colleagues [93] defined low-intensity treatments in their review by therapeutic contact of less than six hours and required studies to provide interventions that not only involved reducing depressive symptoms, but also intended to improve self-management of depression and prevention of relapse and recurrence in the long-term. Therefore, many studies addressing treatments delivered through remote technologies were probably excluded from the review due to more than six hours of contact.

Currently, the majority of studies in this field investigate the efficacy of guided or unguided internet-based interventions during the acute phase of major depression treatment. Meta-analyses demonstrate that CBT provided over the internet (iCBT) is superior to control groups (waiting list, usual care) in reducing depressive symptoms at posttreatment, but not during follow-up [95, 96], and shows less risk of deterioration compared to control groups

[97]. Meta-analyses also demonstrate that guided internet interventions lead to greater symptom reduction and fewer dropouts compared to unguided interventions [98, 99]. Moreover, iCBT seems to be equally effective to face-to-face CBT in reducing depressive symptoms [100–102], and iCBT might be equally effective regarding adherence although completion rates in face-to-face CBT were higher compared to iCBT [103].

Some studies also address the relapse-preventive character of internet-based interventions, indicating that iCBT is associated with fewer relapses compared to control group after 24 months follow-up [104], and also indicating that iCBT is at least as effective as group-based face-to-face CBT also during three years of follow-up [105]. One trial compared iCBT with e-mail therapy and found that the majority of participants showed only minimal depressive symptoms over 3.5 years of follow-up comparable across treatment conditions, indicating that individuals with mild to moderate major depression might benefit from such internet interventions in the long-term [106].

By contrast, evidence regarding internet-based interventions in individuals with persistent depressive symptoms is limited. One study reanalyzed data of participants who received iCBT for their depression, and compared outcomes of participants showing chronic symptoms (more than two years) with non-chronic participants [107]. Chronicity of symptoms did not predict treatment outcome (level of depressive symptoms at posttreatment), and neither did both groups differ regarding their change in depressive symptoms from pre- to posttreatment, but chronically depressed patients achieved full recovery less often. Another study provided two patients with CBASP over the internet ('CBASP@home') in order to maintain gained therapeutic successes over three months after patients had terminated a 12 week inpatient CBASP program [108]. For each of the nine sessions, the patient completes the 'situational analysis', which is a key procedure of the CBASP program, and receives feedback from his/her psychotherapist via a secured sever. This study describes two case reports and concludes that CBASP@home might be accepted and feasible for supporting the

patient in transferring the gains from inpatient treatment to everyday life situations, and by this, preventing relapse and improving approaches of long-term care for PDD patients [108].

2.4.4 Telephone-based interventions

Whilst internet-based interventions are mostly provided as stand-alone interventions that require little or no contact between patient and therapist, one might wonder if development of a sound therapeutic relationship is possible in this context, as visual and auditory cues are missing [109]. Delivering psychotherapy by telephone might approach this challenge, as all auditory information is maintained, and moreover, since it might be considered a valuable further approach to providing many patients with treatment, due to its low-intensity character in terms of low costs, overcoming barriers and practicability in everyday life [110]. While a personal contact between patient and therapist is guaranteed, delivering telephone therapy is more suitable in terms of arranging the time and place of therapy than traditional face-to-face settings. Telephone therapy as a stand-alone treatment in depressive disorders has been investigated only within the field of acute depression so far, and is associated with reducing depressive symptoms compared to control groups [111], and shows comparable effectiveness (e.g., with regard to level of depressive symptoms) as well as lower dropout rates than face-to-face settings in CBT [112–114]. Moreover, therapeutic alliance in telephone-based CBT for acute depression was found to be equal to face-to-face CBT [115]. Studies also indicate a relative cost-effectiveness of telephone-based interventions, with 36% lower costs per sessions compared to face-to-face settings [116].

Besides evidence on effectiveness, little attention has been paid to the patients' perspectives of new technologies in mental health care. One study assessed patient acceptance and resistance to telephone-based care (mostly CBT), and found wide heterogeneity between participants' evaluations [117], which the authors did not only attribute to technical

limitations of the medium alone. Moreover, they highlight the relevance of perceived 'adequacy of fit' between CBT and telephone delivery, assuming that dissatisfied participants might have had a discrepancy between medium telephone and their individual constructs of what therapy represents. However, the majority of participants accepted telephone for the delivery of CBT components [117].

As outlined above, there is some evidence that telephone might be an adequate medium for delivering CBT to acutely depressed individuals. Evidence on *persistently or recurrently depressed individuals* as well as evidence on *continuation and maintenance treatments* delivered by telephone is even more limited. A recent study provided an eight week self-help intervention which also included a weekly 15-minute telephone support to recurrently depressed individuals currently in full or partial remission or recovery [118]. Participants receiving this intervention (added to care as usual) showed fewer relapses or recurrences and a greater reduction in depressive symptoms over 12 months compared to participants receiving care as usual only. Participants in this study were not required to have terminated an acute treatment beforehand and thus, the provided intervention is not considered a continuation treatment per definition. However, this intervention included working on specific relapse and recurrence prevention strategies and a personal prevention plan, which are key components of continuation treatments [39].

To our knowledge, there is only one study available which investigated *a telephone-based psychotherapeutic intervention during the continuation treatment phase*. This program was offered to individuals with substance abuse disorders who had completed an intensive four week outpatient program before entering the telephone-based twelve-week continuation treatment [119]. Participants in the telephone condition received an initial face-to-face session followed by one 15-minute phone call each week, having the opportunity to join a weekly support group during the first four weeks of treatment. The telephone condition showed higher rates of total abstinence and was less expensive per client from a societal perspective

during follow-up, compared to more intense face-to-face standard interventions [120]. The authors were also interested in the moderating effect of a composite risk factor, which was calculated based on the amount of addictive substances and response to previous acute treatment. They found that participants with low to moderate risk-scores showed better outcomes in the telephone condition, while participants with higher risk-scores showed better outcomes in face-to-face conditions [119]. The authors conclude that although mechanisms of change in telephone-based interventions are not yet known, patients who achieved stabilization might benefit from such a continuation program, which is focused on goals, more convenient compared to face-to-face settings due to flexibility in time and location, and has less interference with responsibilities as employment or child care.

The above outlined studies, although limited in number and methodological quality, indicate that telephone might be an adequate medium for delivering continued psychotherapeutic care to depressed patients who responded to or remitted after a previous intensive treatment. There is more research needed to confirm effectiveness of telephone-based interventions compared to face-to-face settings regarding clinical outcome measures. In case of equal effects, telephone-based interventions might be associated with lower costs and more flexibility in time and location compared to face-to-face settings, and by using this technology, representing considerable potential for overcoming several barriers to providing and receiving care [121], and as a consequence, preventing relapse and recurrence.

With respect to limited evidence in low-threshold long-term interventions for individuals being at high risk of relapse, we developed a telephone-based continuation treatment for patients with recurrent or persistent depression who previously responded to an acute psychotherapy, and evaluated the feasibility and acceptance of this program within a pilot study, as described in study 2 of this thesis.

2.5 Summary

The previous chapters outline that several effective pharmacological and psychological treatments exist to prevent relapse and recurrence of depression. The majority of these studies focus on effects of the entire treatment program as measured by reliable change between pre- and posttreatment, and most of these studies were conducted during the acute treatment phase of major depressive disorder. However, relapse and recurrence rates tend to remain high even after successful acute therapy. Whilst providing several short-term treatments with intervals of (more or less) well-being in-between is one way of care, the question is whether this treatment concept corresponds to the needs of a chronically impaired patient. This thesis assumes that long-term care in terms of continuation and maintenance treatments might be the more appropriate way of approaching the recurrent and persistent character of depressive disorders. But effects of continued and maintained treatments, especially in severely depressed individuals, are quite inconclusive due to a limited number of available studies and marked heterogeneity between these studies. All three studies presented in this thesis address relapse-preventive efforts of treatments for depressive disorders to sustain remission and recovery in the long-term. Each of the studies takes the potential recurrent or persistent character of depression into account, indicating that all treatment phases should focus intensively on relapse-preventive strategies, and that continuation and maintenance treatments might be offered to individuals being at higher risk of relapse.

3 Specific research questions

As introduced in the theoretical background, researchers are interested in finding answers to the question of why individuals suffering from depression frequently experience relapse and recurrence despite receiving evidence-based treatments. Besides biological components that might contribute to the recurrent and chronic character of depression, factors

within the health care system might also contribute to the course of depressive symptoms. This thesis addresses the latter approach, by optimizing access to and investigating effects of interventions for depressive disorders within different treatment phases (see figure 2) to sustain remission and recovery in the long-term.

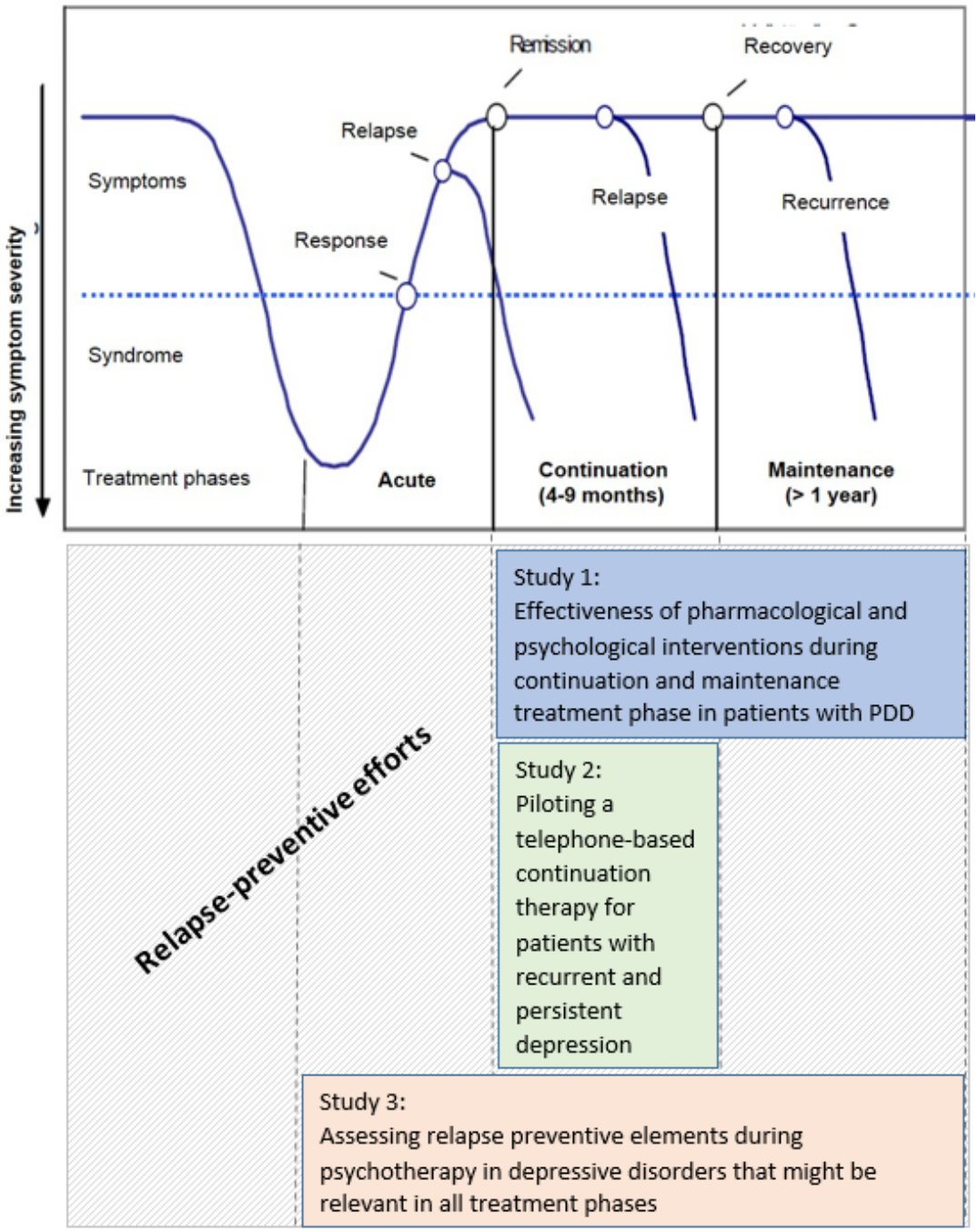

Figure 2. Graphic representation of the three studies presented in this thesis.
Ordered by treatment phase. The upper part was retrieved and adapted from DGPPN et al. (2009).

Study 1 illustrates the current evidence on the general effectiveness of continuation and maintenance treatments for individuals suffering from persistent depressive disorder (PDD) by means of a systematic review and meta-analysis. This study addresses a) whether psychotherapy and antidepressant medication (ADM) are more effective than no treatment or placebo, respectively, and b) whether both treatments are considered equally effective in direct comparison and as add-on treatments (i.e., combination of psychotherapy and ADM compared to each treatment alone). We were interested in relapse/recurrence and dropout rates as primary outcomes, but also in several secondary outcomes including quality of life and adverse events, each at the end of the intervention and during follow-up. As we already expected to find a limited amount of available studies in this field, we conducted a subsequent study, which aims at developing telephone-based continuation therapy for PDD patients who had previously responded to acute psychotherapy, to help patients sustain remission in the long-term.

Study 2 addresses the question if such a program is feasible and accepted by therapists and their patients suffering from recurrent or persistent depression. As use of technology is considered a promising approach to provide many people with mental health care [110], we were especially interested in the acceptance of the telephone in this context, combined with evaluation of the impact of length and frequency of therapeutic phone calls. Moreover, we wanted to determine how implementation of the continuation concept was realized, because continuation therapy is no simple extension of acute therapy, but rather supports patients in transferring already learned strategies to everyday life situations and over time. As delivering continued care in high-risk patients by telephone is a new treatment concept, we decided to first determine feasibility and acceptance of this program with the help of qualitative means within a pilot study.

Finally, *study 3* focuses on therapist behavior during psychotherapy, which might contribute to the relapse-preventive effect of psychotherapy in (several) depressive disorders.

This study explores if there are relapse-preventive efforts other than those implemented in existing adherence and competence scales [80, 81] that can be observed during video-taped psychotherapy sessions. For this purpose, we developed a new measure for assessing relapse preventive elements during psychotherapy ('the KERI-D'), which aims at fostering the transfer from therapy to life after termination of therapy. We were interested in the degree of inter-rater and retest reliabilities and in content validity as measured by clinical and scientific experts, as well as in associations of KER-D subscales with clinical outcome data.

In the following chapters, all three studies are described in detail without further comments in-between. Main results, limitations, and contributions to relapse prevention are first discussed separately for each study, followed by a general discussion of all three studies reviewing relevance and scope regarding the prevention of relapse and recurrence and sustaining remission and recovery in the long-term in depressive disorders.

4 Empirical studies

4.1 Comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder (Cochrane review)[2]

4.1.1 Abstract

Background. Given the high rates of relapse and recurrence of persistent depressive disorder (PDD) following response to acute treatment, long-term continuation and maintenance therapies are frequently needed.

Objectives. To summarize empirical evidence on the effectiveness of psychological, pharmacological and combined continuation and maintenance treatments for PDD.

Search methods. Search of the Cochrane Depression, Anxiety and Neurosis Review Group's specialized register of randomized controlled trials (CCDANCTR), PsycINFO, PSYNDEX, MEDLINE, EMBASE, CENTRAL, and grey literature up to December 2016. We also searched reference lists of included studies and contacted the first author of all included studies.

Selection criteria. We included randomized (RCTs) and non-randomized controlled trials (NRCTs) in adults with formally diagnosed PDD, receiving pharmacological, psychological, or combined continuation and maintenance interventions.

Data collection and analysis. Data were extracted independently by two reviewers. The primary efficacy outcome was relapse/recurrence rate of depression. The primary acceptance outcome was dropping out due to any reason other than relapse/recurrence. Random effects meta-analyses were performed using risk ratio (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes.

[2] For a similar version of this chapter see [122].

Main results. We included 10 studies (seven RCTs, three NRCTs) involving 840 participants in this review, from which five studies investigated continuation treatments and five studies investigated maintenance treatments. The most common comparison was antidepressant medication versus pill placebo. Participants taking antidepressant medication were significantly less likely to relapse or to suffer from a recurrent episode compared to participants in the placebo group at end of intervention (RR = 0.41, 95% CI = 0.21 to 0.79; participants = 383; studies = 4; I^2 = 54%). Overall dropout rates (four RCTs, N = 386) did not differ significantly between participants in the medication and placebo group (RR = 0.90, 95% CI 0.39 to 2.11). All other comparisons were addressed in no or very few studies. However, regarding psychological treatments the few studies indicate that continued or maintained psychotherapy could be a useful intervention compared to no treatment or antidepressant medication. Overall, the included studies were at low to moderate risk of bias.
Authors' conclusions. Antidepressants seem to be superior to placebo in continuation and maintenance treatment regarding relapse/recurrence. For all other comparisons the body of evidence was too small to draw final conclusions, although continued or maintained psychotherapy might be effective compared to no treatment. A need for conducting more psychological interventions is obvious. Further studies should address health related quality of life and adverse events more precisely, as well as assessing follow-up data.

4.1.2 Plain language summary

Long-term treatment for people with persistent depression

Why is this review important?

Depressive disorders that persists for at least two years cause considerable problems. Even after successful treatment, they frequently recur. Common treatments are antidepressant drugs and psychological treatments (talking therapies) or a combination of both.

Long-term treatments should prevent the recurrence of depressive symptoms.

Who will be interested in this review?

People with persisting depression (> two years), friends, families, and carers. General practitioners, psychiatrists, clinical psychologists, psychological therapists, and pharma-cists.

What questions does this review aim to answer?

In adults with persistent depression who improved with acute treatment:

Is receiving continued antidepressant medicine, psychological treatment, or a combination of both more effective in preventing recurrence of depression compared to placebo (a pre-tended treatment) or care as usual? Is receiving continued antidepressant medicine, psychological treatment, or a combination of both equally accepted as receiving placebo or usual care? Is one treatment more effective or more accepted than another?

Which studies does the review include?

We searched medical databases and other sources to find all relevant studies completed up to December 2016. The studies had to compare antidepressant treatment, psychological treatment, or a combination of both, with each other, with placebo, or with care as usual for preventing recurrence of depression in adults diagnosed with persistent depression. We included 10 studies involving 840 participants. Five studies compared antidepressant medicine with placebo. The other comparisons were only addressed in zero to two studies.

What does the evidence from the review tell us?

The risk of depression returning in participants receiving a placebo (instead of antidepressant medicine) was 34%. In comparison to that, participants remaining on antidepressant medicines had a significantly lower risk for recurrence of 14%. The continued treatment lasted between four months and two years. Antidepressant were as well accepted as placebo. As studies on the long-term effects of medication are lacking, recommendations on the necessary duration of medication treatment cannot be drawn.

The benefits of psychological therapies or combined treatment remained unclear, due to the small number of studies. Overall, the included studies were of moderate or high methodological quality.

What should happen next?

This review provides evidence that continued antidepressant medication (compared to pill placebo) can reduce the risk of depression recurring in adults with persistent depression. However, only a few studies have been done. Further studies should especially address psychological and combined long-term treatments.

4.1.3 Background

Description of the condition

Persistent forms of depression that last for two years or longer represent a substantial proportion of depressive disorders [17, 123–125]. Within the literature, four subtypes can be distinguished: (1) dysthymia, (2) chronic major depression, (3) recurrent major depression with incomplete remission between episodes, and (4) double depression [35]. Dysthymic disorder is defined as a condition with mild depressive symptoms persisting for at least two years. Major depressive episode, chronic type, refers to a more severe condition that meets full criteria for major depression continuously for a minimum of two years. Patients who have recovered to the point at which they no longer meet full criteria for a major depressive episode but continue to experience significant symptoms for at least two years are referred to as recurrent major depression with incomplete remission between episodes. The superimposition of a major depressive episode on antecedent dysthymia is referred to as double depression [20]. In the DSM-5 [13], the new diagnostic category of persistent depressive disorder was introduced subsuming dysthymic as well as chronic major depressive disorders.

The mean length of persistent depression is between 17 and 30 years [17, 18], and the lifetime prevalence for persistent depressive disorders is estimated to range from 3% to 6% in the Western world [19–21]. In comparison to acute forms of depression, persistent depressive disorders are associated with longer treatment duration, increased loss of physical wellbeing, increased comorbidity, more severe impairments in social, psychological and emotional functioning, increased health care utilization, and more frequent suicide attempts and hospitalizations [17, 36]. Thus, persistent depression is likely to make a large contribution to the high burden of disease that is associated with unipolar depression according to disability-adjusted life years (DALYs) [126].

Description of the intervention

Overall, a large number of different interventions exist for the treatment of unipolar depression, including psychological, pharmacological, and combined psychological and pharmacological therapies. Evidence from randomized controlled trials as well as meta-analyses suggests that these interventions are effective in the acute treatment of depression, including persistent forms of depression [43, 54–58, 73, 127]. Still, there is also evidence that a relevant amount of patients does not respond to treatment, does not reach complete remission and develops persisting residual symptoms in the long run [128]. It is estimated that probably half of the people suffering from depressive disorders are developing a chronic course [5].

Moreover, acute phase treatments often fail to prevent relapse (which is defined as the return of symptoms of depression before a full remission has been achieved) and recurrence (which is defined as the appearance of another new episode of depression after full remission of a previous episode has been achieved) in major depression. For example, after scheduled termination of acute phase cognitive therapy (CT), relapse/recurrence rates were found to be 29% in the first year and 54% in the second year [12]. In this same study, even when other

depression-specific psychological therapies and even higher doses of pharmacotherapy were used after the acute-phase treatment, relapse and recurrence rates were still found to be high [12]. Besides, there are studies showing that 30 to 50% of patients considered to be remitted still have to deal with residual depressive symptoms [129].

Thus, following response to acute treatment, long-term continuation and maintenance therapy is required to protect patients from relapse or recurrence of symptoms. Continuation treatments are defined as treatments given to currently remitted patients (remission is defined as depressive symptoms dropping below case level) or to patients that previously responded to an antidepressant treatment. Maintenance therapy is given during recovery (which is defined as remission lasting longer than six months) [8, 45]. The German National Clinical Practice Guideline for Unipolar Depression [6] recommends a combination of pharmacotherapy and psychological therapy as acute phase treatment for patients suffering from persistent forms of depression. Additionally, a continued psychological therapy and/or pharmacotherapy is recommended to prevent relapse and recurrence. Specifically, the type of treatment which was successful in the acute phase is recommended to be continued [6, 45, 130]. However, the recommendations concerning the continuation of therapy are based on unipolar depressive patients in general, specific recommendations regarding patients with persistent depressive disorders are lacking.

Hence, a systematic search of evidence regarding the effectiveness of pharmacological, psychological and combined pharmacological and psychological therapies as continuation and maintenance treatments for patients suffering from persistent forms of depression is needed.

How the intervention might work

Acute treatments aim to reduce depressive symptoms and re-establish psychosocial functioning. In comparison, continuation and maintenance treatments aim to maintain (or improve) the psycho-functional status reached by acute treatment, and to reduce the likelihood of relapse and recurrence in the long-term [6]. Therefore, continuation and maintenance treatments are considered to be more than a pure extension of acute treatments, because continuation/maintenance treatments differ in frequency and content over the course of the illness in comparison to acute treatments.

Psychological continuation and maintenance interventions are offered usually less frequently than acute psychological therapy, aiming to monitor symptoms and to integrate techniques and strategies into daily life in the long-term [6]. Different programs targeting the prevention of relapse and recurrence focus on a range of effect mechanisms. Cognitive therapy (CT) approaches focus on the generalization of skills achieved during acute therapy [131] or the cognitive content of negative thinking [38]. Mindfulness-Based Cognitive Therapy (MBCT) was especially developed to reduce relapse and recurrence in depression [47, 48] and teaches people to deal with negative feelings and thoughts as a part of their lives through becoming aware of negative cognitive patterns. Maintenance Interpersonal Psychotherapy (IPT) aims to complement skills gained in the acute phase therapy and teaches patients to take responsibility in the prevention of future episodes by recognizing and preventing stressing environmental and social circumstances [49]. Still, it remains challenging to completely understand the mechanisms of preventing relapse and recurrence [49].

The exact therapeutic mechanisms of antidepressants are still critically discussed [50]. Most antidepressants seem to increase the concentrations of monoamine neurotransmitters (e.g., serotonin or noradrenaline) in the synaptic cleft [51]. However, the effect of most antidepressants fully develops after some weeks, indicating that neurophysiological changes of brain tissue (e.g., changes in sensitivity and frequency of receptors), occurring in the

presence of a constant level of active ingredients, are necessary for permanent improvement. Depending on the type of active ingredient, antidepressants can have mood-enhancing, anxiolytic or sedative effects and are able to increase or decrease inner drive. Moreover, the placebo effect is of particular importance in the treatment of depression. There are studies assuming that the more severe the depressive symptoms are, the greater the benefit of antidepressants seem to be compared to placebo [132, 133]. However, a recent meta-analysis performed on patient-level data regarding the response to antidepressant medication showed that initial depression severity and outcomes were similarly related in treatment and placebo groups [134].

A number of studies have shown that the risk of relapse or recurrence of depression is associated with residual symptoms following acute treatment phases. These findings lead to the therapeutic goal of sustained remission and recommendations of international treatment guidelines to continue antidepressant medication after acute phase treatment [45, 130].

Why it is important to do this review

Research focusing on the prevention of recurrence of depression was identified as a top priority in the recent project "Depression: asking the right questions" [22]. The high prevalence and the severe personal, societal and economic consequences of persistent depressive disorder [17] underline the need for adequate treatment strategies. Growing evidence indicates that persistent depressive disorder responds well to several acute interventions such as combined psychological and pharmacological treatments, although the number of randomized controlled trials is still limited [127]. Yet, given the high rates of relapse and recurrences of depression following response to acute treatment, long-term continuation and maintenance therapy are of great importance [49].

The effectiveness of continuation and maintenance therapies for depression has been supported by several randomized controlled trials [65, 135–140]. A meta-analysis on relapse prevention with antidepressant drug treatment of depressive disorders [42] showed that continued antidepressant medication produced a robust reduction in relapse. Another meta-analysis [12] summarizes the findings of long-term effects of cognitive behavioral therapy (CBT). Patients who responded to acute treatment and continued to receive CBT showed a significant reduction in relapse and recurrence rates in comparison to inactive as well as active controls.

Although the vast majority of evidence addresses acute treatments for persistent depressive disorder or long-term treatments for acute depressive episodes, some studies have been performed to address the effectiveness of long-term treatments of persistent depressive disorder [62–70]. Until now, no systematic review on the comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder is available.

In summary, this systematic review may be of high relevance due to the following reasons: Persistent depressive disorders have a high prevalence and serious personal, societal, and economic consequences. No evidence synthesis is available on continuation and maintenance treatments of persistent depressive disorders. High quality evidence synthesis is needed for clinical guideline recommendations and their implementation in clinical practice.

Objectives

To assess the effects of pharmacological and psychological continuation and maintenance treatments for persistent depressive disorder, in comparison with each other; placebo (drug/attention placebo/non-specific treatment control); and treatment as usual. In addition, to assess the effects of combined psychological and pharmacological continuation and maintenance treatments, in comparison with either of these treatments alone.

4.1.4 Methods

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs), and non-randomized controlled trials (NRCTs) were included in the systematic review. NRCTs were considered in this review as we expected a limited number of RCTs. No restrictions regarding other design characteristics were applied. There were no cross-over or cluster RCTs eligible for inclusion in this review, however future versions of this review could consider including these trials.

Types of participants

We considered participants from the age of 18 years of any gender and ethnicity for inclusion. Participants who have a diagnosis of persistent depressive disorder or have had this diagnosis before their last previous acute treatment were included. The diagnosis of depression needed to rely on a formal classification system, such as the International Classification of Diseases (ICD) [141] or the Diagnostic and Statistical Manual of Mental Disorders (DSM) [13]. Participants needed to be either currently remitted from persistent depressive disorder or needed to have at least partially responded to an acute intervention (at least 25% symptom reduction from baseline) at the beginning of the continuation or maintenance treatment. Participants described as "treatment resistant" were included if they fulfilled the formerly mentioned criteria. As the distinction between subtypes of persistent depressive disorder (chronic major depression, dysthymia, double depression, or recurrent depression without a complete remission between episodes) is controversial, inclusion was primarily driven by the duration of the existing depressive disorder. Consequently, studies investigating participants with chronic major depression, dysthymia, double depression, or

recurrent depression without a complete remission between episodes were included if the target disorders are or have been of at least two years' duration. Studies reporting to investigate "chronically depressed" participants without fulfilling these criteria (e.g., less than two years duration) were excluded.

Studies focusing exclusively on persistently depressed participants with a specific concurrent mental or somatic disorder were excluded – as we assume that the interventions in these kinds of studies (primarily) address the comorbid condition and are not focused exclusively on persistent depression. Studies that did not define specific concurrent mental or somatic conditions as inclusion criteria but reported on comorbidities in addition to the persistent depressive disorder were included. No restrictions based on setting were made. Studies, in which both participants with persistent and acute forms of depression were included, were only considered, if data were reported separately for the persistent subgroup (or if 80% or more of the total sample has a diagnosis of persistent depression). If randomization was based on the total sample, studies were included and categorized as non-randomized controlled trials.

Types of interventions

Experimental intervention

Pharmacological, psychological, and combined continuation and maintenance interventions were considered. Continuation treatments were defined as treatments given to currently remitted individuals or to individuals that previously responded to an antidepressant treatment, whereas maintenance treatments were defined as treatments given to people who are currently recovered. Continuation/maintenance treatments needed to be started within one year after termination of an acute treatment. We considered all interventions that satisfied these definitions. Additionally, studies that did not report all the above mentioned criteria but

reported data on interventions that were clearly labeled as “continuation” or “maintenance” treatments were considered.

We considered pharmacological interventions including the oral administration of classified antidepressants: tricyclic antidepressants, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, alpha2-receptor-antagonists, selective noradrenalin dopamine reuptake inhibitors, melatonin receptor agonists and serotonin 5 HT2C receptor antagonists, as well as non-classified antidepressants (Trazodone), lithium, Hypericum perforatum, and antipsychotic drugs, as these drugs can be used (alone or in combination) in treating different forms of depression [6].

Psychological therapies had to fulfil the following criteria: The intervention must be based on a scientific theory (described in detail and/or manualized and/or referenced). At least one contact between therapist and participant either face-to-face or via telecommunication technologies (e.g., online therapy) must take place. Thus, for example, the general dissemination of information material in form of leaflets in waiting rooms will not be considered as a psychological therapy. The intervention must consider the personal needs of the participant or a group of participants and must be individually tailored in an interpersonal process. Thus, group therapies will be included. Concerning psychological therapies, we considered behavior therapy/behavior modification, cognitive behavioral therapy, third wave cognitive behavioral therapies, psychodynamic therapies, humanistic therapies, integrative therapies, systemic therapies, and other psychologically-oriented interventions (based on the definition of the Cochrane Common Mental Disorders Group) for inclusion. Combined interventions included the administration of one or more pharmacological agents combined with one or more psychological therapy.

Somatic (e.g., electroconvulsive therapy, vagus nerve stimulation, acupuncture), non-pharmacological (e.g., physical exercise, bright light therapy), and organizational (e.g., case

management) interventions were not considered as including too many different interventions was likely to result in large clinical and methodological heterogeneity.

Comparator intervention

Both controlled and comparative effectiveness studies were included. The comparators were: pharmacological placebo (participants received placebo pills), attention-placebo/nonspecific control (participants received a treatment that involved nonspecific psychosocial factors or assessment only), treatment as usual (TAU), (other) psychological therapy, (other) pharmacological treatment, (other) combined psychological/pharmacological therapy.

Types of outcome measures

Primary outcomes

1. Relapse or recurrence rate of depression, preferentially defined as a) fulfillment of formal diagnostic criteria for depression (DSM, ICD), or as b) exceeding a cut-off on a depression symptom rating scale used by the authors, specifically i) the Hamilton Depression Rating Scale (HAM-D) [142], ii) the Montgomery -Åsberg Depression Rating Scale (MADRS) [143], iii) the Beck-Depression-Inventory (BDI) [144], iv) the Inventory of Depressive Symptomatology (IDS) [145], v) the Patient Health Questionnaire (PHQ) [146], or vi) any other depression symptom scale. Due to the long tradition of depression research, most instruments used in clinical trials are usually psychometrically sound. Such measures were preferred throughout the review (either referenced and/or sufficient psychometric quality reported). 2. Dropout due to any reason.

Secondary outcomes

3. Symptom severity of depression at the end of treatment (metric outcome of depression scale as defined above). 4. Health related quality of life (e.g., WHO Quality of

Life [WHOQOL] [147]). 5. Dropout due to adverse events. 6. Experiencing any adverse event. 7. Serious adverse events.

Definition of adverse events and side effects are inconsistent [148, 149]. In this review, adverse events are defined as any negative event occurring during or after treatment in relation a patient whereas side effects are defined as any adverse event that can be attributed to a lege artis invervention. Adverse events leading to serious consequences like death, mortal danger, hospitalization or disability are referred as serious adverse events [150].

The primary outcome time point was 'end of intervention' (regardless of the duration of the intervention). Additionally, outcome was planned to be evaluated at the time point 'one year after the end of intervention' providing that enough data would be available. If one-year-data were not available, we planned to use data that ranged between 6 and 18 months after the end of intervention with a preference for the time that was closest to one year after the end of intervention. However, just one study provided follow-up data 12 weeks after end of intervention. If more than one diagnostic definition and/or depression symptom rating scale was available (concerning outcome 1. Relapse or recurrence rate of depression), the presented hierarchy was used to select measures (priority starting with a) fulfillment of formal diagnostic criteria, continuing with b) i) (HAM-D), b)ii) (MADRS) etc.).

Search methods for identification of studies

Electronic searches

1. The Cochrane Common Mental Disorders Group maintains a specialized register of randomized controlled trials (RCTs), the CCMD-CTR (description in Appendix A, see p. 192). The CCMD-CTR was searched for study records using the following controlled search terms (condition only): ("chronic depression" or "dysthymia" or "dysthymic disorder" or "persistent depressive disorder" or "recurrent depression") 2. The CCMD-CTR was searched for reference records using a more sensitive set of terms (condition only) : ("chronic*

depress*" or "double depress*" or dysthymi* or (depress* NEAR2 recurr*) or "persistent depressive disorder"):ti,ab,kw,ky,mh,mc,emt [Key: ti=title; ab=abstract; kw=keywords; ky=additional keywords; mh=MeSH terms; mc=MeSH checkwords;emt=EMTREE terms]. Records were screened for continuation and maintenance trials. 3. As the review includes both RCTs and NRCTs, complementary searches were conducted on the following bibliographic databases using relevant subject headings and search syntax', appropriate to each resource: OVID PsycINFO (search strategy listed in Appendix A, see p. 192), PSYNDEX, OVID MEDLINE, OVID EMBASE, CENTRAL (Cochrane Library).

Databases were searched from 1970 onwards (EMBASE from 1980) until December 2016; no other restriction on language or publication status was applied to the searches. Records retrieved from the CCMD-CTR and PsycINFO searches were screened prior to running other database searches and the search strategies were validated to prevent the retrieval of too many irrelevant references (for example, following the first search we considered including the specific terms for 'maintenance' or 'continuation' of treatments for persistent depressive disorder appropriate).

Searching other resources

The following sources of grey literature were searched: ProQuest Dissertations and Theses Database (http://www.proquest.com/; retrieved August 11, 2015), Depression. The treatment and management of depression in adults [45], S3 Guideline/National Clinical Practice Guideline. Unipolar Depression [6], Canadian Network for Mood and Anxiety Treatments (CANMAT). Clinical guidelines for the management of major depressive disorder in adults [151], Open Grey (http://www.opengrey.eu/; retrieved August 11, 2015).

As all relevant journals are included in the bibliographic databases being searched no further handsearches in journals were conducted. The reference lists of all included studies and relevant systematic reviews were checked to identify additional studies missed from the

original electronic searches (for example, unpublished or in-press citations). A cited reference search was also conducted on the Web of Science. The first author of all included studies was contacted for information on unpublished or ongoing studies or to request additional trial data.

Data collection and analysis

Selection of studies

Two review authors [KM, SL, RM, or AJ] independently screened titles and abstracts for inclusion of all the potential studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve' (ineligible). We retrieved the full-text study reports/publications and two review authors [KM, SL, or RM] independently screened the full-texts and determined studies for inclusion. Reasons for exclusion of the ineligible studies were recorded. We resolved any disagreement through discussion or, if required, we consulted a fourth person [AJ]. We identified and excluded duplicate records and we collated multiple reports that relate to the same study so that each study rather than each report was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management

We used a data collection form, which has been piloted on at least one study in the review, to extract study characteristics and outcome data. Two independent review authors [KM, SL, or RM] extracted study characteristics and outcome data from included studies. We extracted the following study characteristics: study design, time of randomization, total duration of study, location, study setting, and date of study (year), number of participants (N), mean age, age range, % female, diagnostic subgroup, mean age of onset, length of current/last episode, number of previous episodes, intervention, comparison, type of acute treatment

previous to continuation/maintenance treatment, primary and secondary outcomes specified and collected, and time points reported, funding of the trial.

We noted in the 'Characteristics of included studies' table (see Appendix B, see p. 196) if outcome data were not reported in a usable way. We resolved disagreements by consensus or by involving a third person [KM, SL, or RM]. One review author [SL] transferred data into the Review Manager file [152]. We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author [KM] spot-checked study characteristics for accuracy against the trial report.

Main comparisons

Seven main comparisons were chosen from the list of possible comparisons based on clinical importance and expected frequency of the comparisons in clinical trials:

1. pharmacological continuation and maintenance therapies versus placebo
2. pharmacological continuation and maintenance therapies versus treatment as usual (TAU)
3. psychological continuation and maintenance therapies versus attention placebo/nonspecific control
4. psychological continuation and maintenance therapies versus treatment as usual (TAU)
5. psychological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies
6. combined psychological and pharmacological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies alone
7. combined psychological and pharmacological continuation and maintenance therapies versus psychotherapeutic continuation and maintenance therapies alone.

Assessment of risk of bias in included studies

Two review authors [KM, SL, or RM] independently assessed risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [153]. We resolved any disagreements by discussion or by involving another author [KM, SL, or RM]. We assessed the risk of bias according to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, other bias. We judged each potential source of bias as high, low or unclear and provided a supporting quotation from the study report together with a justification for our judgment in the 'Risk of bias' table. We summarized the risk of bias judgments across different studies for each of the domains listed. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table. The ROBINS-I tool [154] for assessing the quality of non-randomized studies in meta-analyses was used to assess the quality of non-randomized controlled trials. We included no cluster-randomized trials, however in future versions of this review recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomized trials in cluster-randomized trials should be considered [153]. The risk of bias was considered in sensitivity analyses. Moreover, we took the risk of bias into account when interpreting the treatment effects.

Measures of treatment effect

Dichotomous data

In order to increase clinical applicability of the findings, the relative risk of relapse/recurrence was calculated for the primary outcomes, as they are more likely to help clinicians to make informed decisions in specific clinical situations. For rare outcomes (adverse events) or endpoints with highly varying baseline rates, odds ratios were estimated.

None of the included studies in this review used time-to-event data, however in future versions of this review primary studies should consider pooled hazard ratios for calculations.

Continuous data

We analyzed continuous data as mean differences (MD). In this review, all studies used the same rating scale for depression severity (HAM-D), however if in future versions of the review there are different scales used across the studies, standardized mean differences (SMD) should be analyzed. We entered data presented as a scale with a consistent direction of effect. We undertook meta-analyses only where this was meaningful, i.e., if the treatments, participants and the underlying clinical question were similar enough for useful pooling. We planned to narratively describe skewed data reported as medians and interquartile ranges – if effect size calculation is not possible. This procedure was not necessary in this review, however in future versions of this review this could be considered.

Unit of analysis issues

Cross- over and cluster-randomized trials

As we expected a small number of overall available studies, data from cross-over trials and cluster-randomized trials were planned for inclusion in the analysis, regardless of the level of randomization. None of the studies in this review was either a cross-over or a cluster-randomized trial. However, in future versions of this review, cluster-randomized trials should include direct effect estimates of the primary studies, only if they were obtained from analyses that accounted for the clustering in the data (e.g., using a multilevel model). Otherwise, the effect estimates should be approximated using an inflated standard error that incorporates the design effect [153]. Concerning cross-over trials, only the first comparison (pre-crossover) meeting our inclusion criteria should be used from cross-over trials.

Studies with multiple treatment groups

Concerning studies with multiple treatment groups, for each of the main objectives addressed in our review, only data from the comparison of interest were considered. If the study provided more than one comparison of interest for one of the main objectives, we planned to divide the number of participants in the arm used several times by the number of arms for all analyses to avoid including participants more than once in the analysis. However, this procedure was not necessary to implement in our analyses but should be considered in future versions of this review.

Dealing with missing data

In case of missing or unclear data, we contacted corresponding authors or study sponsors in order to obtain key study characteristics and missing numerical outcome data when possible (e.g., when a study was identified as abstract only). We documented all requests and correspondences. For all studies, we planned to calculate effect sizes using the intention-to-treat principle, i.e., analyzing all subjects allocated to the respective study arm. For the primary outcome, all randomized participants were included in the analyses (when possible) irrespective of how the authors of the primary studies defined their intention-to-treat (ITT) sample. For all other outcomes the definition of the intention-to-treat sample provided by the authors were followed. In case, no ITT data were available, we used the data provided.

Assessment of heterogeneity

Statistical heterogeneity between study results were tested for significance using Cochran's Q-test and quantified using the I^2 statistic [155]. Results were visually displayed as forest plots. We expected considerable clinical heterogeneity between studies. I^2 values in the range of 0% to 40%: might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent substantial heterogeneity, and 75% to 100%:

considerable heterogeneity. Based on this classification, we considered I^2 values in the range of 50 to 100% as relevant statistical heterogeneity that is to be further explored. As "thresholds for the interpretation of I^2 can be misleading, since the importance of inconsistency depends on several factors" [153], this was only a rough orientation. Therefore, we decided on a case-by-case-basis if the determined heterogeneity needed to be further explored.

Assessment of reporting bias

Possible reporting biases and small-study effects were tested using visual examination of funnel plots (when useful). Egger's test [156] was planned for test of publication bias but could not be applied in this review, as it requires at minimum 10 studies per comparison.

Data synthesis

All analyses were performed by applying a random effects model [157]. We used random effect models rather than fixed effect ones, because we assumed that the included studies would not be functionally equivalent and would show considerable clinical (concerning population, intervention) and methodological (concerning quality) heterogeneity. Results are visually displayed as forest plots. If it was not possible to combine studies via meta-analysis, a narrative summary was provided.

Subgroup analysis and investigation of heterogeneity

In order to identify possible treatment effect moderators, a priori defined subgroup analyses (in case of categorical predictors) or meta-regression analyses (in case of metric predictors) were planned for the primary outcomes. Due to the little amount of included studies we were not able to undertake these analyses. However, in future versions of this review, differences between subgroups should be tested formally [158–160], and all meta-regression analyses should be performed using the restricted maximum likelihood estimate method, a recommended random effects approach that accounts for residual between-trial heterogeneity [161].

The following variables were planned to be considered in subgroup analyses: **Subtype of persistent depressive disorder** (dysthymia vs. other): A possibly moderating effect of subtype would suggest that a distinction between these subtypes might be used for allocation of patients to treatments (differential indication). On the other hand, a possible homogeneity of effects across subtypes may suggest that a distinction is of little relevance in the day-to-day practice. Dysthymia will be tested against other subtypes as dysthymia is assumed to be the most frequently mentioned subtype. **Mean age of onset**: The age of onset is known as a relevant predictor, it should be assessed if patients with early onset need different treatments. **Applied intervention** (cognitive behavioral therapies vs. other, SSRIs vs. other): As experience shows, cognitive behavioral approaches/SSRIs are the most frequent forms of psychological therapies/antidepressants to be studied. Therefore, we decided to test these approaches vs. other approaches. Evidence on the best available treatments (in case of considerable differences) is indispensable for guideline recommendations. **Duration of continuation/maintenance treatment** (weeks): For guideline recommendations and clinical practice, it is indispensable to know, if different treatment durations result in different outcomes, e.g., if longer treatments lead to better outcomes.

In case of considerable heterogeneity between study results that cannot be explained by the a priori defined subgroup and meta-regression analyses, a series of a posteriori (explorative)

meta-regression analyses should be performed to identify sources of heterogeneity. A priori and a posteriori analyses should be clearly labeled as such.

Sensitivity analysis

Sensitivity analyses were performed excluding studies with a high or unclear risk of bias (separately for each of the seven domains according to the risk of bias-tool of the Cochrane Handbook, when possible) and/or outlying findings. Results were contrasted to those acquired with data from all studies in order to control for possible effects of study quality on pooled effects. Additional sensitivity analysis were planned: 1) excluding trials without a randomization on person level (second phases of cross-over trials, NRCTs, and cluster-randomized trials) and 2) excluding trials without (re-)randomization immediately before the continuation/maintenance phase in order to control for possible design effects. However, due to the small number of included studies we were not able to apply additional analyses, but this procedure should be considered for future versions of this review.

Summary of findings table

Summary of findings tables were provided for one comparison: effectiveness of pharmacotherapy versus placebo for persistent depressive disorder. Summary of findings tables include a summary of the quality of evidence, the magnitude of effects of the according intervention and a summary of available data on the primary outcomes (relapse/recurrence and dropout due to any reason). Findings were expressed as measures of risk ratio and absolute risk. The GRADE approach was used to assess the quality of the body of evidence [162].

4.1.5 Results

Description of studies

Results of the search

We conducted searches between December 2015 and December 2016, retrieving 4489 rec-ords from the CCDANCTR studies and references registers. Following this, we ran a cross-search on OVID MEDLINE, EMBASE and PsycINFO, together with a search on CENTRAL (Cochrane Library), retrieving an additional 929 records after exclusion of duplicates. Screening several sources of grey literature (Open Grey, ProQuest, ICTRP, clinicaltrials.gov), reference lists of relevant systematic reviews and studies, and correspondence with authors of included studies yielded additional 732 records. After removal of duplicates, two review authors (SL, KM, RM, or AJ) independently screened 5418 records by title and abstract and excluded 4899 records as they did not meet inclusion criteria or were untraceable. Each of the remaining 519 full-texts was checked independently by two out of three review authors (SL, KM, or RM) for eligibility. We included 17 publications for the qualitative synthesis, and out of this pool we used 10 studies for the quantitative synthesis. The PRISMA flow diagram displays the details of the selection process (figure 3).

Included studies[3]

Qualitative analysis: We included 17 publications, describing five continuation and five maintenance studies in the qualitative analysis. Three publications (Keller 1998b, Keller 2000, Marin 1994) described the acute phases of the included continuation and maintenance studies, one publication was a study protocol (Rush 1998) and three publications (Berndt 2000, Kocsis 1997, Kocsis 2002) provided additional analyses on the studies of Keller 1998 and Koran 2001. Thus, these seven publications were used to extract data missing in the main

[3] For reasons of clarity and comprehensibility, from now on the included studies will be addressed by the form ‚First author, year of publication', e.g., Koran 2001. The respective complete references can be found in Appendix B, see p. 197.

publications. Apart from that, they are not further addressed here. The quantitative syntheses is based on 10 studies described below.

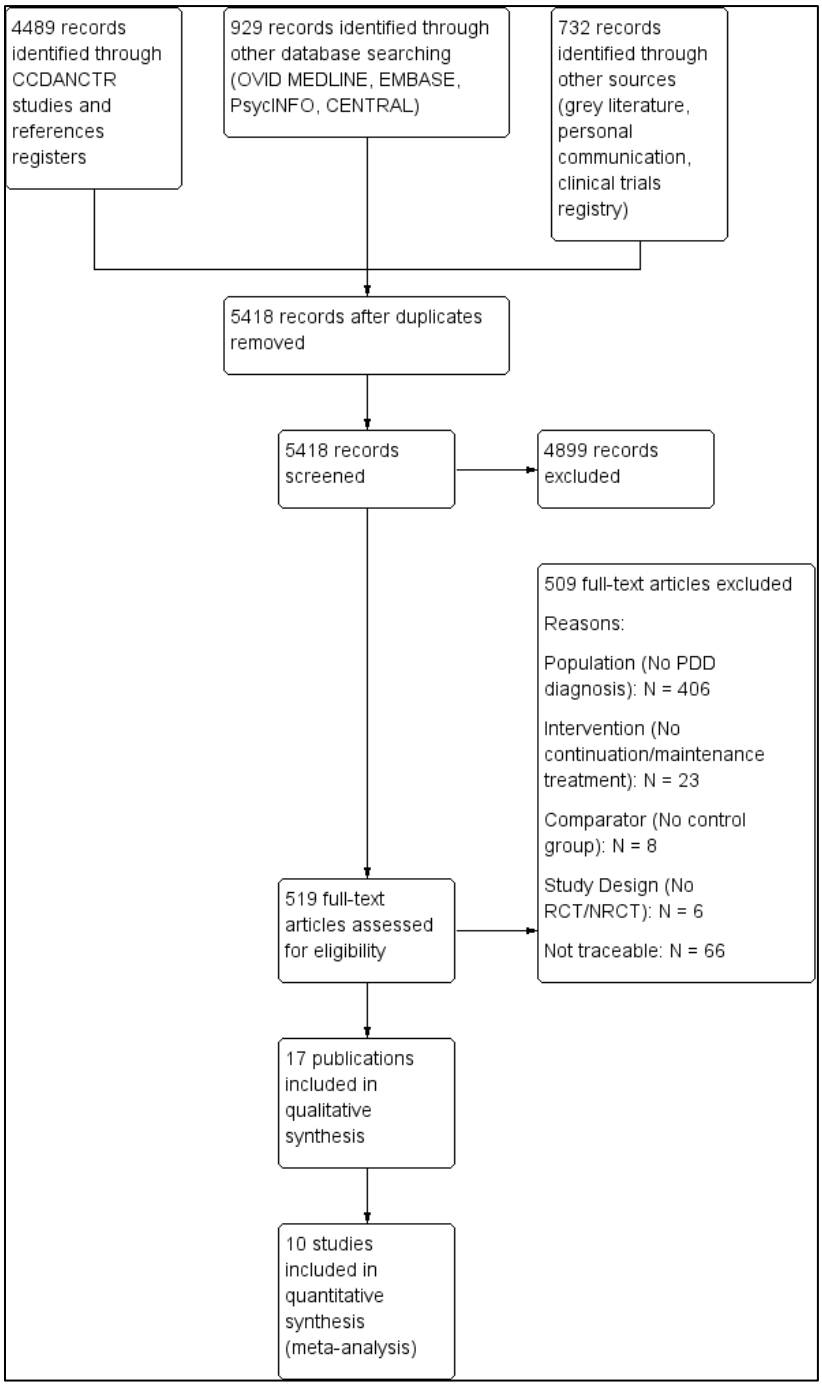

Figure 3. Study flow diagram

Quantitative analysis: We included 10 studies (following five acute treatment studies) in the quantitative analysis of this review. There are partially overlapping patient groups

between the different continuation/maintenance treatment studies that followed one acute treatment study. However, these studies focus on different comparisons and were not included in the same analyses. One exception are the studies of Kocsis 1996 and Miller 2001. These two studies focused on the same comparison (desipramine versus placebo) during the maintenance phase, but analyzed different diagnostic subgroups. Whilst Miller 2001 analyzed solely dysthymic participants, Kocsis 1996 included additionally participants with a chronic major depressive episode and double depression. Both studies share the group of dysthymic participants, although just partially as Miller 2001 included also dysthymic participants not involved in Kocsis 1996. Two studies (Harrison 1986; Hellerstein 2001) investigated solely continuation treatments. The other eight studies (Koran 2001; Keller 1998; Gelenberg 2003; Kocsis 2003; Klein 2004; Kocsis 1996; Miller 2001; Kocsis 1995) followed three acute treatment studies, and investigated both continuation and maintenance treatments. For an overview of included studies and corresponding acute treatment studies see table 1.

Comparisons

We predefined seven relevant comparisons:

1) Pharmacological continuation and maintenance therapies versus placebo. Five of ten studies included comparisons of an antidepressant medication with a pharmacological placebo (Keller 1998; Harrison 1986; Gelenberg 2003; Kocsis 1996; Miller 2001). Two of these five studies (Kocsis 1996; Miller 2001) compared desipramine vs. placebo in the maintenance phase, but used different subgroups for analyses (see table 1).

2) Pharmacological continuation and maintenance therapies versus treatment as usual (TAU). There were no studies comparing pharmacological therapies versus TAU.

3) Psychological continuation and maintenance therapies versus attention placebo/nonspecific control. One study (Klein 2004) compared psychotherapy versus assessment only.

4) Psychological continuation and maintenance therapies versus treatment as usual (TAU). There were no studies comparing psychological therapies versus TAU.

5) Psychological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies. One study with three treatment arms (Kocsis 2003) compared pharmacological, psychological and combined continuation therapy.

6) Combined psychological and pharmacological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies alone. The study of Kocsis 2003 with three treatment arms (see above) as well as the study of Hellerstein 2001 provided data on this comparison.

7) Combined psychological and pharmacological continuation and maintenance therapies versus psychotherapeutic continuation and maintenance therapies alone. The study of Kocsis 2003 with three treatment arms (see above) provided data on this comparison.

8) Pharmacological continuation and maintenance therapies versus other pharmacological continuation and maintenance therapies (post hoc). This comparison was not predefined, but as two studies (Koran 2001 and Kocsis 1995) provided data on this comparison, this comparison was included a posteriori.

Table 1 *Overview of included studies*

Related acute phase study	**Study ID**	**Treatment arms**	**Continuation/Maintenance (treatment duration)**	**Study Design**	**Diagnosis**
Keller 1998b	**Koran 2001**	Sertraline Imipramine	Continuation (16 weeks)	NRCT	chronic major depressive disorder, double depression
	Keller 1998	Sertraline Placebo	Maintenance (76 weeks)	RCT	chronic major depressive disorder, double depression
Harrison 1986	**Harrison 1986**	Phenelzine Placebo	Continuation (26 weeks)	RCT	dysthymia, double depression
Keller 2000	**Kocsis 2003**	Nefazodone CBASP Combination	Continuation (16 weeks)	NRCT	chronic major depressive disorder, double depression, recurrent depressive disorder with incomplete interepisode remission
	Gelenberg 2003	Nefazodone Placebo	Maintenance (52 weeks)	RCT	chronic major depressive disorder, double depression, recurrent depressive disorder with incomplete interepisode remission
	Klein 2004	CBASP Assessment only	Maintenance (52 weeks)	RCT	chronic major depressive disorder, double depression, recurrent depressive disorder with incomplete interepisode remission
Hellerstein 2001	**Hellerstein 2001**	Fluoxetine Fluoxetine + Group Psychotherapy	Continuation (16 weeks)	RCT	dysthymia
Marin 1994	**Kocsis 1995**	Imipramine Desipramine	Continuation (16-20 weeks)	NRCT	dysthymia, double depression
	Kocsis 1996*	Desipramine Placebo	Maintenance (104 weeks)	RCT	chronic major depressive disorder, dysthymia, double depression
	Miller 2001*	Desipramine Placebo	Maintenance (104 weeks)	RCT	dysthymia

** These groups are partially overlapping (see above).*

Design

Two studies used a randomized controlled parallel group design to investigate the continuation treatment phase (Harrison 1986, Hellerstein 2001). Three studies (Koran 2001, Kocsis 2003, Kocsis 1995) investigated a continuation treatment within a non-randomized controlled trial, i.e., the patients continued to receive the same treatment being effective during acute treatment. Each of these three studies was followed by maintenance treatments applying a randomized controlled parallel group design (Keller 1998; Gelenberg 2003; Klein 2004; Kocsis 1996; Miller 2001). Continuation treatments lasted between 16 and 26 weeks, maintenance treatments between 52 and 104 weeks. All 10 studies involved preceded acute treatments in their study design (see table 1).

Sample Size

Study size varied largely. The two studies investigating solely a continuation treatment randomized 12 participants (Harrison 1986) and 40 participants (Hellerstein 2001). Two studies randomized between 329 participants (Kocsis 2003) and 386 participants (Koran 2001) for the continuation phase and re-randomized between 82 participants (Klein 2004) and 161 participants (Keller 1998) for the subsequent maintenance phase. Another study (Kocsis 1995) randomized 73 participants to the continuation phase and re-randomized between 27 participants (Miller 2001) and 53 participants (Kocsis 1996) to the subsequent maintenance phase.

Setting

Two studies were multicenter (Harrison 1986, Hellerstein 2001) and five were singlecenter studies (Koran 2001; Keller 1998; Kocsis 2003; Gelenberg 2003; Klein 2004). One study was conducted multicenter during the continuation treatment (Kocsis 1995) and

continued singlecenter during the maintenance phase (Kocsis 1996, Miller 2001). All studies were conducted in the US and used an outpatient setting for treatment.

Inclusion criteria

All studies required the participants to meet DSM criteria for persistent depressive disorder by the time of entering the study, i.e., start of acute treatment. Two continuation treatment studies included dysthymic participants only (Harrison 1986; Hellerstein 2001), whereby the latter one focused on early onset dysthymic participants. Whilst Koran 2001 and Keller 1998 included participants with either a chronic depressive episode or double depression, Kocsis 2003, Gelenberg 2003 and Klein 2004 additionally included participants with recurrent depression with incomplete interepisode remission. Kocsis 1995 analyzed participants with either dysthymia or double depression in the continuation treatment phase. The subsequent maintenance treatment phase (Kocsis 1996; Miller 2001) included participants with either chronic major depressive disorder, dysthymia or double depression, whereby Miller 2001 analyzed only dysthymic participants.

All studies used explicit response or remission criteria for entry into continuation or maintenance phases. Participants were required to show at least clinical response or partial remission, scoring below 15 on the Hamilton Rating scale (HAM-D) (Kocsis 2003; Gelenberg 2003; Klein 2004) or to range between a score of seven and 12 on the HAM-D (Kocsis 1996; Miller 2001). Harrison 1986 required the participants to reach a score of 1 or 2 ("very much improved" or "much improved") on the Clinical Global Impression (CGI). Koran 2001 and Keller 1998 required participants to fulfil both a HAM-D score of 15 or less and a CGI score of less than 3 (i.e., no more than mild depression). One study additionally defined specific remission criteria based on the Longitudinal Interval Follow-up Evaluation (LIFE) for participants with double depression (Koran 2001), scoring with 1 (no symptoms) or 2 (some symptoms) during four weeks. Six studies determined response or remission with at least 50%

decrease of symptoms compared to acute phase baseline scores (Koran 2001; Keller 1998; Kocsis 2003; Gelenberg 2003; Klein 2004; Miller 2001), and one study with at least 40% reduction of symptoms (Hellerstein 2001).

For the studies investigating continuation treatments, participants had to achieve the defined response or remission criteria directly at the end of acute treatment (Kocsis 2003; Hellerstein 2001) or had to maintain the specific score for the last four weeks before entering the continuation phase (Koran 2001). For the studies investigating maintenance treatments, participants had to continue their response or remission throughout the end of continuation treatment for being eligible to enter the maintenance phase (Keller 1998; Gelenberg 2003; Klein 2004; Kocsis 1996; Miller 2001). Participants included in the studies had to be aged between 21 and 65 (Koran 2001; Keller 1998; Hellerstein 2001) or between 18 and 75 years (Kocsis 2003; Gelenberg 2003; Klein 2004).

Patients' characteristics

Whilst one study (Harrison 1986) reported that the majority of included participants were in their thirties or fourties, all other studies provided mean age scores of participants varying between 36 and 45 years of age. Harrison 1986 included predominantly female participants (83%), while the proportion of women varied between 50% and 66% in all other studies. Distribution of diagnostic subgroups differed among the included studies, whereby eight studies treated participants of several diagnostic subgroups, and two studies analyzed solely dysthymic participants (Hellerstein 2001, Miller 2001). The number of participants with double depression varied between 23% and 63% (Koran 2001; Keller 1998; Harrison 1986; Kocsis 2003; Gelenberg 2003; Klein 2004; Kocsis 1995; Kocsis 1996). Six studies treated participants with a chronic depressive episode (Koran 2001; Keller 1998; Kocsis 2003; Gelenberg 2003; Klein 2004; Kocsis 1996), of which the amount varied between 11% and 55%. Three studies also treated participants diagnosed with a recurrent depressive episode

with incomplete interepisode remission (Kocsis 2003; Gelenberg 2003; Klein 2004), of which the amount varied between 22% and 29%. Three studies treated also participants with dysthymia, of which the amount varied between 37% and 40% (Harrison 1986; Kocsis 1995; Kocsis 1996).

Data on the mean age of onset were provided in six studies, the mean age of onset ranged from 12.3 to 29.5 years. The mean length of the current/previous episode (data provided in five studies: Gelenberg 2003; Keller 1998; Klein 2004; Kocsis 2003; Koran 2001) was 73.2 to 105.6 months. Four studies (Hellerstein 2001; Keller 1998; Klein 2004; Koran 2001) provided data on the number of previous episodes and reported a mean number of 1.3 to 3.0 episodes.

Exclusion criteria

All five studies described criteria for excluding participants prior to study entry, i.e., before starting the acute treatment of the study program. Six studies excluded participants who failed to respond to either at least one adequate trial of antidepressant medication (Koran 2001; Keller 1998; Harrison 1986) or who failed to respond to three or more previous trials of antidepressant medication and/or at least two trials of empirical supported psychotherapy (Kocsis 2003; Gelenberg 2003; Klein 2004). All studies (except Harrison 1986) excluded participants with serious medical illness, DSM diagnosed axis I disorders (if principal), personality disorders, present psychotic symptoms, or immediate suicidal risk. Five studies excluded participants who took concomitant (psychoactive) medication or who had received electroconvulsive therapy (ECT) either within three months (Koran 2001; Keller 1998) or three years prior to study entry (Kocsis 2003; Gelenberg 2003; Klein 2004). Hellerstein 2001 excluded participants who parallel underwent another psychotherapy, and Koran 2001 and Keller 1998 excluded participants who started another psychotherapy within the previous three months before entering study.

Types of intervention

Antidepressant drugs and drug placebo interventions

Continuation treatment: One continuation treatment study included the comparison of an active antidepressant drug with a pill placebo (Harrison 1986). In this study, the monoamine oxidase inhibitor (MAOIs) phenelzine was used as active treatment for 26 weeks. Participants in the active group received on average 51mg of phenelzine daily. Participants in the placebo group discontinued phenelzine treatment over a period of 14 days by reducing the daily dose by 15mg every 2 to 3 days. Two continuation treatment studies included a direct comparison of two antidepressant medications. Koran 2001 compared sertraline (SSRI) with a dose between 50mg and 200mg per day to imipramine (TCA) with a dose between 50mg and 300mg per day during 16 weeks of treatment. The dose could be adapted by 50mg per day a week depending on the participant's symptoms and side effects. The second study (Kocsis 1995) compared two tricyclic antidepressants during 16 to 20 weeks of treatment. Participants received the same final dose achieved during acute treatment (300mg of imipramine or 200mg of desipramine per day). Two continuation treatment studies included comparisons of antidepressant medication alone versus the combined treatment of medication and psychotherapy. Kocsis 2003 investigated three active treatment arms, including nefazodone (SNDRI) alone, psychotherapy alone (Cognitive Behavioral Analysis System of Psychotherapy), and their combination over 16 weeks. In both medication arms, participants received between 300mg and 600mg nefazodone per day. Hellerstein 2001 compared fluoxetine (SSRI) alone with the combined treatment of fluoxetine and a group psychotherapy over 16 weeks. Participants in both arms received between 20mg and 80mg of fluoxetine per day.

Maintenance treatment: Four maintenance treatment studies included the comparison of an active antidepressant drug with a pill placebo (Keller 1998; Gelenberg 2003; Kocsis 1996; Miller 2001). Of these four, two studies (Kocsis 1996, Miller 2001) analyzed the same comparison (desipramine vs. placebo) but with focus on different diagnostic subgroups. All studies used antidepressants of different classes. In Keller 1998, the participants in the active treatment group received a flexible daily dose of 50 to200mg of the selective serotonin reuptake inhibitor (SSRI) sertraline hydrochloride for 76 weeks. Participants in the placebo arm reduced the sertraline dose by 50mg every week and received placebo substitution. Gelenberg 2003 used nefazodone, a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI) at the same dose being effective during the previous continuation phase (300mg and 600mg per day) over 52 weeks. Participants in the placebo arm received identical (but inactive) tablets without any stepwise reduction between continuation and maintenance phase. Kocsis 1996 and Miller 2001 used the tricyclic antidepressant (TCA) desipramine over 104 weeks as maintenance treatment. Participants in the active group maintained the dose (75-350mg/day) of the previous continuation phase. Participants in the placebo arm reduced their dose by 25% per week during the first month of maintenance treatment and subsequently started a treatment with identical placebo pills.

Types of psychological therapies

Three studies were identified that investigated psychotherapeutic treatments, two continuation treatment studies and one maintenance treatment study. Kocsis 2003 examined the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) (McCullough 2000) during the 16 week-continuation phase. Participants received six sessions of manualized CBASP, both in the CBASP and the combined treatment arm. The continuation treatment study of Hellerstein 2001 compared a fluoxetine (SSRI) only group with a group receiving fluoxetine in combination with a manualized group psychotherapy in a 16 week continuation

phase. The latter group received treatment according to an unpublished manual of Cognitive-Interpersonal Group Psychotherapy for Chronic Depression (CIGP-CD), combining cognitive and interpersonal approaches. Up to 10 participants formed a group with weekly meetings of 90 minutes. Klein 2004 investigated the comparison of CBASP versus assessment only in the 52 week-maintenance phase which followed the study of Kocsis 2003 (see above). Participants in the CBASP group received one session every four weeks for a total of up to 13 sessions, and were evaluated by an independent evaluator every four weeks. Participants in the assessment only group attended the project coordinator and the independent evaluator also every four weeks, hence received some attention but no active treatment.

Process evaluation of psychological treatments

Information on process evaluation was inferable from one continuation treatment study (Hellerstein 2001) and one maintenance treatment study (Klein 2004). Hellerstein 2001 involved two clinical psychology PhD students with extensive psychotherapy training for conducting the group therapy in the continuation treatment phase. On a weekly basis, these two students met a senior psychiatrist supervisor during two months for reviewing how to conduct the treatment with the CIGP-CD treatment manual. By the start of the study, sessions with the participants were audiotaped and supervised weekly for adherence to the manual. Information on the CBASP sessions in the maintenance treatment study was inferable from the main publication (Klein 2004). Additional information was received from the publication of the acute treatment phase (Keller 2000). The CBASP sessions were all videotaped and conducted by psychotherapists with at least two or five years of experience (dependent on last degree achieved). The therapists underwent a two-day training workshop with James P. McCullough (founder of CBASP) including an evaluation of two videotaped pilot cases before starting treatment with study participants. Throughout the maintenance phase, therapist's adherence to treatment procedures was assessed biweekly by

reviewing videotapes by designated supervisors at each site. These supervisors were directly supervised by James P. McCullough. Treatment adherence was measured using a CBASP specific rating scale developed by McCullough (McCullough 2000). In case of nonadherence, an immediate meeting with the respective therapist was scheduled and opportunities for improvement were discussed.

Types of outcome measures

Primary outcomes

The primary efficacy outcome were rates of relapse or recurrence of depression, defined by either exceeding a specific score on the HAM-D or on the severity of the CGI, by fulfilling DSM criteria for a major depressive episode (MDD), and/or by clinical judgement of the research team during a predefined range of time.

Two continuation studies applied criteria for relapse, either scoring below a satisfactory response during four weeks (Koran 2001) or scoring three or more on the CGI during two weeks (Harrison 1986). In the maintenance treatment study of Keller 1998, participants had to fulfill DSM criteria for a MDD during three consecutive weeks, a CGI rating of three or more, and an increase of at least four points on the HAM-D (compared to maintenance baseline) to be diagnosed as having a recurrence. One week later, a senior investigator had to determine the diagnosis within a clinical interview to confirm relapse. Two other maintenance treatment studies (Kocsis 1996; Miller 2001) defined a participant's recurrence by a score of 12 or more on the HAM-D and a score below 60 on the GAS on three consecutive ratings within four weeks. Also, if a participant fulfilled these criteria on just one rating but was considered to need urgently alternative treatment, the participant was rated as being recurred.

One continuation treatment study (Kocsis 2003) and two maintenance treatment studies (Gelenberg 2003; Klein 2004) applied the same criteria for recurrence, as they

followed the same acute treatment study (Keller 2000). This three studies required the participants to score 16 or higher on the HAM-D, to fulfill DSM criteria for a MDD on two consecutive visits and to undergo a clinical interview with a senior investigator confirming recurrence. These three studies also applied another definition in case a participant scored 16 or more on the HAM-D but did not fulfill MDD criteria or discontinued before a second visit for clarification. Then, senior investigators reviewed the data of such participants at the end of study, discussed and decided if and at what time a MDD had occurred and if the participant could be considered to have recurred. Two studies did not address relapse or recurrence as an outcome (Hellerstein 2001, Kocsis 1995).

The primary safety/acceptability outcome was dropout due to any reason other than recurrence. Nine studies reported overall dropout rates. Most of the studies also reported reasons for dropout (see section "secondary outcomes"). One study (Miller 2001) did not report any dropout rates.

Secondary outcomes

Metric outcomes of depression severity scales and quality of life measures were reviewed as secondary efficacy outcomes. In six studies changes in severity of depressive symptoms from pre- to posttreatment on the HAM-D were reported (Koran 2001; Keller 1998; Harrison 1986; Gelenberg 2003; Klein 2004; Hellerstein 2001). Three studies included quality of life measures (Koran 2001; Keller 1998; Hellerstein 2001). The continuation treatment study of Koran 2001 reported data on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), a self-report measure obtaining the degree of enjoyment and satisfaction in different areas of daily functioning. In the subsequent maintenance treatment study, Keller 1998 used the 36-item short-form health survey (SF-36), and reported data on three subscales (social functioning, role limitations owing to emotional problems, role limitations owing to physical health problems) in a further publication (Kocsis

2002). In Hellerstein 2001, the Satisfaction With Life Scale (SWLS), a self-report measure of subjective life satisfaction, was used. Only in this study follow-up outcome data (both for the HAM-D and the SWLS scores) 12 weeks after end of intervention were reported.

Measures of safety, i.e., dropout due to adverse events and the occurrence of any or severe adverse events were also reviewed. Five of ten studies reported dropout due to adverse events other than recurrence, and all of these studies compared antidepressant medication with placebo or another medication (Keller 1998; Koran 2001; Harrison 1986; Gelenberg 2003; Kocsis 1995). Reasons for such dropout were either side effects, insufficient response, intercurrent illness or dispute with staff. Two studies reported the occurrence of any adverse events, including side effects (e.g., headache, insomnia, sexual problems) for the majority of participants (Keller 1998) and side effects (especially sleep disturbances and sexual problems) for all participants in the medication arm (Harrison 1986), although no data were reported for the placebo group in the latter study.

Excluded studies

The major reason for exclusion of studies was the non-fulfilment of the diagnosis "persistent depressive disorder" (see study flow diagram; figure 3, p. 55). Some studies involved participants with recurrent depressive disorder with complete interepisode remission (e.g., Jarrett 2013), other studies involved in fact also chronic forms of depression, but the percentage of chronic forms was less than 80% (e.g., Thase 2001) or no separate analyses of diagnostic subgroups of persistent depression were provided (e.g., Petersen 2010), respectively. Other studies were excluded because they did not apply clear response or remission criteria for participants to be eligible for entering continuation/maintenance treatment, i.e., all participants from the acute phase could take part in the following treatment phases (e.g., Schramm 2017).

Risk of bias in included studies

Of the 10 studies included, seven were randomized controlled trials (RCTs) and three were non-randomized controlled trials (NRCTs). These three NRCTs were continuation treatment studies (Koran 2001; Kocsis 2003; Kocsis 1995), and were labelled as NRCTs for this review as the acute phase responders were not re-randomized for the continuation treatment. The RCTs were rated with the Risk of Bias-Tool on a three point scale (low/high/unclear risk) (see figure 4 and 5). The NRCTs were rated with the ROBINS-I tool (Sterne 2016), using a five point scale (low/moderate/serious/critical/unclear risk) (see figure 6 and 7).

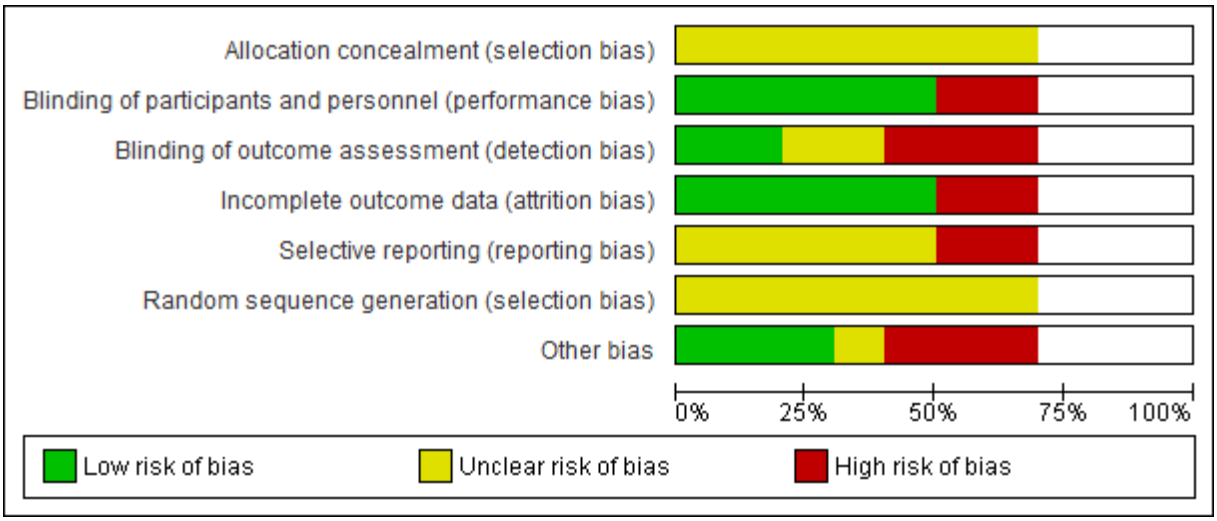

Figure 4. Risk of bias graph RCTs
Review authors' judgements about each risk of bias item presented as percentages across all included seven RCTs. Blank space in rows containing no information indicate missing information on the RoB scale for the three NRCTs.

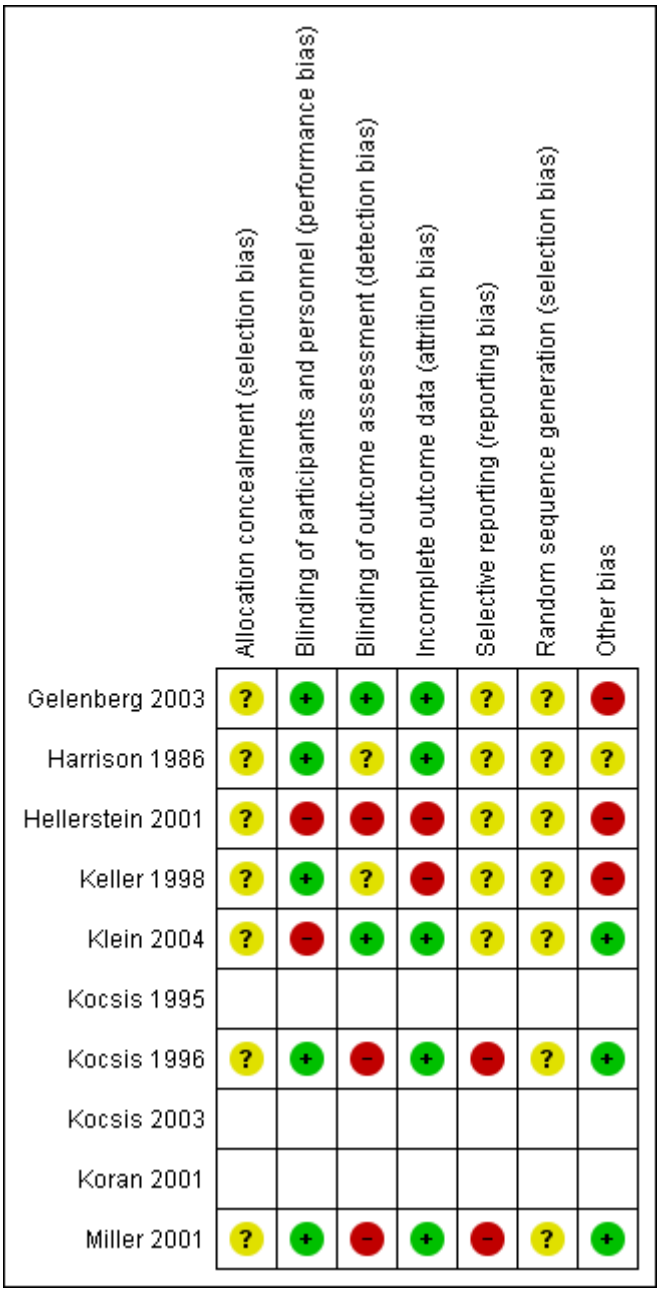

Figure 5. Risk of bias summary RCTs
Review authors' judgements about each risk of bias item for each included RCT (seven studies). Blank space in rows containing no information indicate missing information on the RoB scale for the three NRCTs.

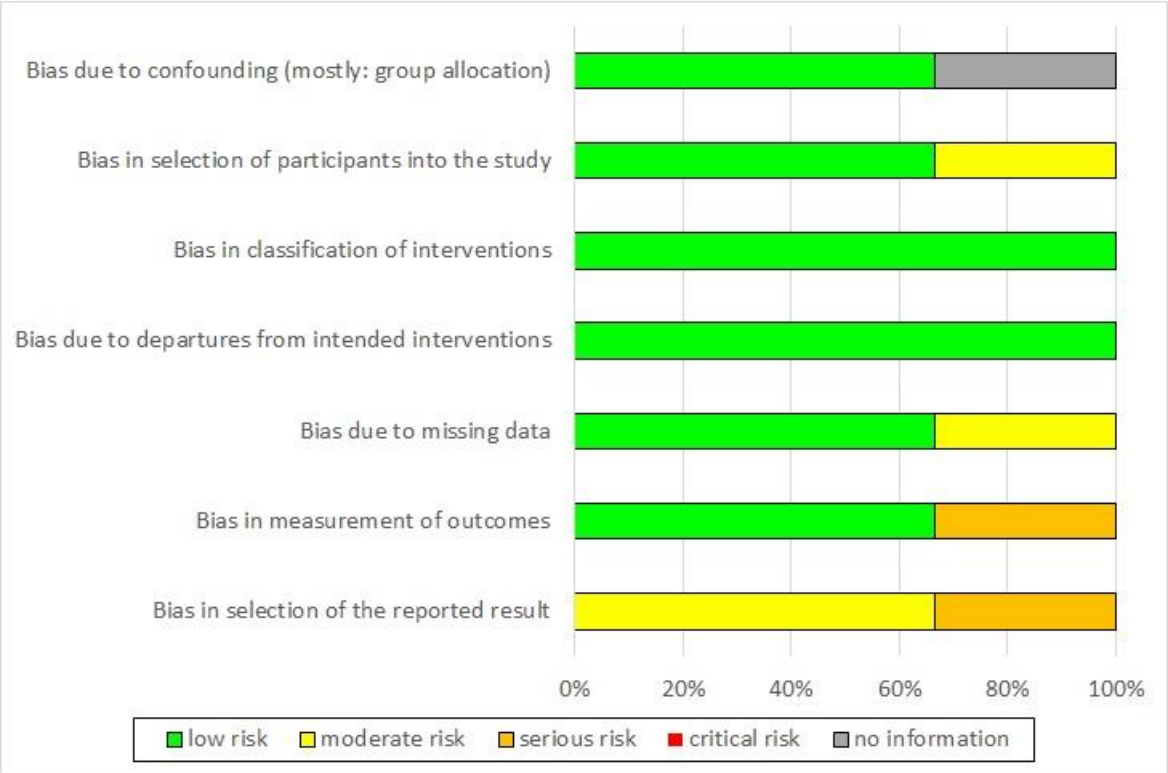

Figure 6. Risk of bias graph NRCTs
Review authors' judgement about each risk of bias item presented as percentages across all included NRCTs (three studies).

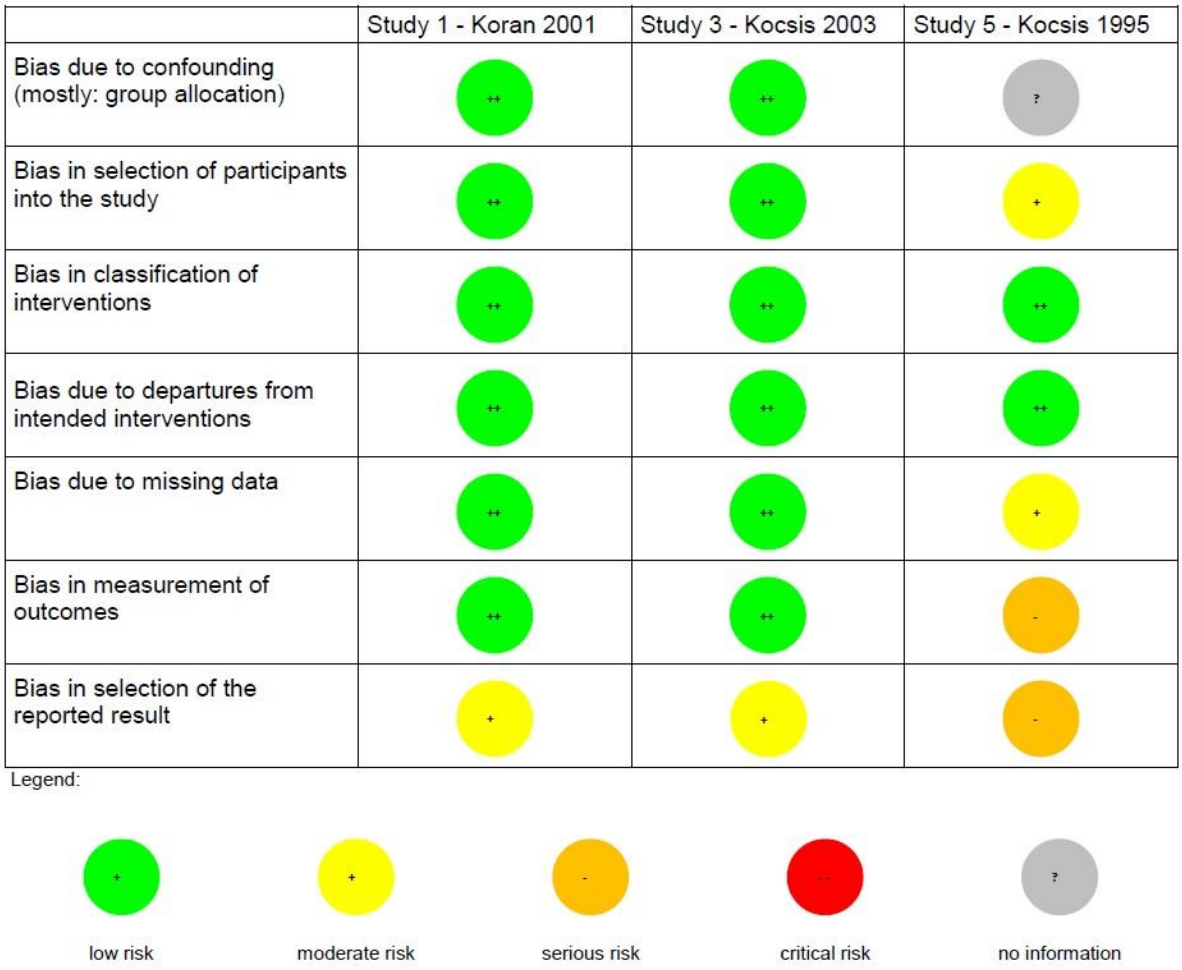

Figure 7. Risk of bias summary NRCTs
Review authors' judgements about each risk of bias item for each included NRCT (three studies).

Risk of Bias in RCTs (7 studies)

Random sequence generation (selection bias). The random sequence generation was described in none of the included RCTs. Hence this domain was rated as unclear risk of bias in all seven RCTs.

Allocation (selection bias). All seven RCTs have an unclear risk of bias concerning allocation as there were no information on the allocation process.

Blinding of participants and personnel (performance bias). Five studies (Keller 1998; Harrison 1986; Gelenberg 2003; Kocsis 1996; Miller 2001) reported that participants and

personnel were blinded (low risk). Two studies (Hellerstein 2001; Klein 2004) were psychotherapy studies. Therefore, participants and personnel were aware of the treatment condition (high risk).

Blinding of outcome assessment (detection bias). In two studies (Gelenberg 2003; Klein 2004), the outcome assessors were independent and blind to the treatment condition (low risk), in two other studies (Keller 1998; Harrison 1986) there was no information on this domain (unclear risk) and in three studies (Hellerstein 2001; Kocsis 1996; Miller 2001) the assessors were study clinicians not blinded to the treatment condition (high risk).

Incomplete outcome data (attrition bias). In five studies (Harrison 1986; Gelenberg 2003; Klein 2004; Kocsis 1996; Miller 2001), the risk concerning incomplete outcome data was low. In these studies, the number of participants with missing data was low (below five percent), there was no missing data or the (main) outcome was reported for all included participants. Two studies (Keller 1998; Hellerstein 2001) had a high risk of bias as the number of participants with missing data was very high, and we considered the used imputation methods (LOCF; last observation carried forward) as rather inadequate for this context (see discussion section).

Selective reporting (reporting bias). Five studies (Keller 1998; Harrison 1986; Gelenberg 2003; Klein 2004; Hellerstein 2001) had an unclear risk concerning this domain. There was no study protocol for the continuation or maintenance treatment available. Nevertheless, the risk of bias was not rated as "high" as outcomes in relevant domains were reported and there was no specific indication for selective reporting. In two other studies (Kocsis 1996; Miller 2001) the risk was assessed as "high" as results were not reported for all applied measures.

Other potential sources of bias. To operationalize the domain of other relevant sources of bias, three subdomains were assessed separately in this review: insufficient treatment

adherence, allegiance bias/conflict of interest, and attention bias. Then, ratings from these three subdomains were summarized to one overall rating of „other potential sources of bias“ for each RCT. If one of these three subdomains indicated a high risk of bias, we assessed the overall rating as “high”. In the case that two (or three) domains indicated an unclear risk and one (or no) domain indicated a low risk, the overall rating was “unclear”. The overall rating was “low risk” if two or three domains indicated a low risk and no or one domain indicated an unclear risk. Three studies (Keller 1998; Gelenberg 2003; Hellerstein 2001) were assessed as having a high risk, especially because conflict of interest was considered very likely (pharmaceutical sponsoring). One study (Harrison 1986) had an unclear risk as information on the three subdomains were mostly lacking. Three studies (Klein 2004; Kocsis 1996; Miller 2001) had a low risk as there was – for example – serum level control to ensure the treatment adherence. Moreover, the investigators ensured that all groups received the same amount of attention and there were – in case of sponsoring from a pharmaceutical company – also other, independent authors involved in the publication.

Risk of bias in NRCTs (3 studies)

Bias due to confounding (mostly: group allocation). Two studies (Koran 2001, Kocsis 2003) were assessed as having a low risk in this domain as participants were randomized before the acute treatment. In one study (Kocsis 1995) there was no information on how participants were allocated to the groups in the acute treatment phase (unclear risk).

Bias in selection of participants into the study. Two studies (Koran 2001, Kocsis 2003) included all eligible participants and described the process of inclusion and the study flow clearly. In the study of Kocsis 1995, participants from three different acute phase treatment protocols with different treatment durations and medication were included, thus the risk in this study was rated as moderate.

Bias in classification of interventions. The intervention status was well defined in all three NRCTs, for example the planned and actual dose of the pharmacological intervention and the number of psychotherapy sessions was described, indicating a low risk.

Bias due to departures from intended interventions. In all three NRCTs, there was no indication for departures from intended interventions, e.g., plasma level checks were performed and the dose range of medication or the number of psychotherapy sessions, respectively, were within the planned range. Therefore, the risk was rated as low.

Bias due to missing data. In the studies of Koran 2001 and Kocsis 2003, the number of participants with missing data was low (less than 5% for the main outcome) and comparable across the intervention groups. The risk was assessed as moderate for the study of Kocsis 1995, as the proportions of participants with missing data differed substantially across the groups, but reasons for dropout were reported.

Bias in measurement of outcomes. The assessment methods were reliable, comparable across treatment groups and performed by trained independent raters in the studies of Koran 2001 and Kocsis 2003. In the study of Kocsis 1995, the frequency of ratings differed across treatment groups and participants as well as raters were aware of the treatment (serious risk).

Bias in selection of the reported result. In the study of Koran 2001, the outcomes correspond to the ones named in the methods section. The study protocol focused solely on the acute phase of the study, and not all measures described in the protocol were reported in the publication of the continuation treatment study (moderate risk). For the study reported by Kocsis 2003, no study protocol was available, but all measures reported in the methods section were also reported in the results section (moderate risk). In the study reported by Kocsis 1995, the risk of bias was rated as serious as not all predefined outcomes were reported.

Effects of interventions

For all comparisons, intention-to-treat (ITT) data were analyzed when possible. Six studies reported ITT data for all outcome measures included in this review. In the other four studies, data for 2% to 10% of the ITT sample were missing for single outcome measures at end of intervention. Missing data were not replaced, calculations are based on the data provided in the publications. Data on the dropout rate (overall dropout and dropout due to adverse events) are consistently based on the complete ITT sample. The only study with follow-up data (Hellerstein 2001) provided data on depression severity at follow-up for the complete ITT sample and data on quality of life at follow-up for 85% of the participants of the ITT sample. Risk ratios (RR) and their 95% confidence intervals (CI) were calculated. When the overall results were significant, the number needed to treat to benefit (NNTB) was also calculated. Mean differences (MD) are presented for continuous data.[4]

1 Pharmacological continuation and maintenance therapies versus placebo

Five studies provided data on this comparison. Keller 1998 compared sertraline (N = 77) with placebo (N = 84), Harrison 1986 compared phenelzine (N = 5) with placebo (N = 7), and Gelenberg 2003 compared nefazodone (N = 76) with placebo (N = 84). Both Kocsis 1996 and Miller 2001 compared desipramine with placebo, analyzing different diagnostic subgroups: Kocsis 1996 (desipramine: N = 28; placebo: N = 25), Miller 2001 (desipramine: N = 14; placebo: N = 13). As Kocsis 1996 and Miller 2001 evaluated partially overlapping groups (see above), only the data of the larger group (Kocsis 1996) were considered here. The sample of Kocsis 1996 was replaced by the sample of Miller 2001 in the sensitivity analyses.

[4] In the following, graphic representations of effects (forest plots) are only displayed if more than one study provided data on the respective comparison.

Primary outcomes

Participants taking antidepressant medication had significant less relapses or recurrences compared to the placebo group at end of intervention, with moderate degree of heterogeneity between these four studies (figure 8). This translates to a NNTB of six. The four included studies were all RCTs. Three of them were maintenance treatment studies (Gelenberg 2003; Keller 1998; Kocsis 1996), while Harrison 1986 was a continuation treatment study. All studies used different antidepressants from varying classes.

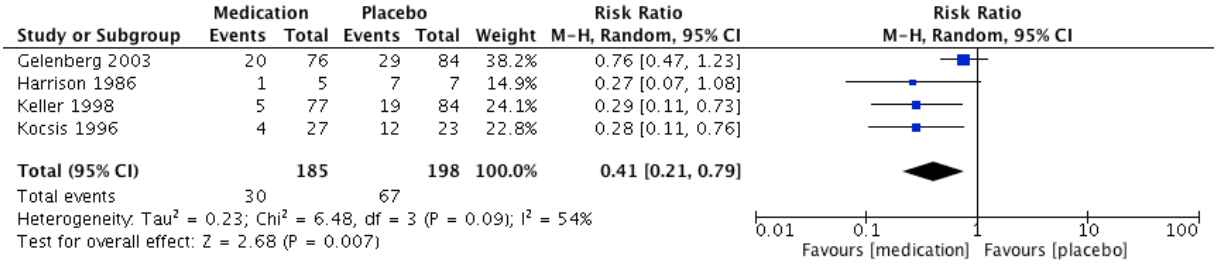

Figure 8. Forest plot of comparison: Medication versus placebo, outcome: Relapse/recurrence.

Four studies provided overall dropout rates at the end of intervention. The four included studies were all RCTs. Three of them were maintenance treatment studies (Gelenberg 2003; Keller 1998; Kocsis 1996), while Harrison 1986 was a continuation treatment study. We found no significant differences between medication and placebo. Heterogeneity was substantial (I^2 = 64%) (figure 9). Two studies (Gelenberg 2003; Kocsis 1996) reported less dropouts in the medication arm, while the other two studies (Keller 1998; Harrison 1986) reported less dropouts in the placebo group.

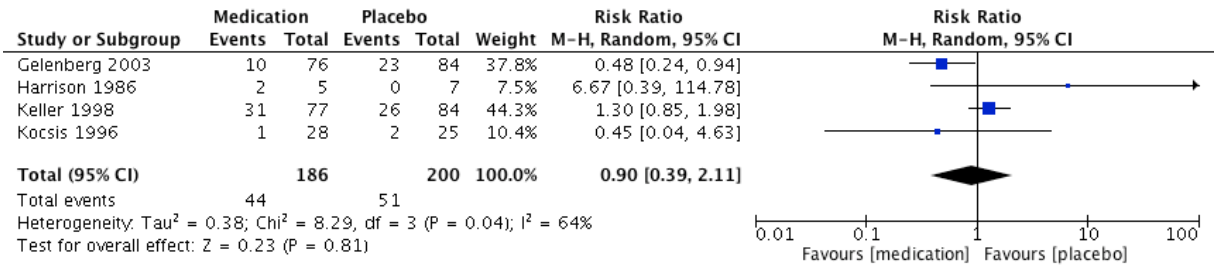

Figure 9. Forest plot of comparison: Medication versus placebo, outcome: Dropout any.

Secondary outcomes

Means and standard deviations (SDs) were available from three RCTs. Two of them were maintenance treatment studies (Gelenberg 2003; Keller 1998), while Harrison 1986 was a continuation treatment study. Participants in the medication arms showed a significantly lower symptom severity on the HAM-D at end of intervention compared to the placebo groups. Heterogeneity was moderate to substantial (figure 10).

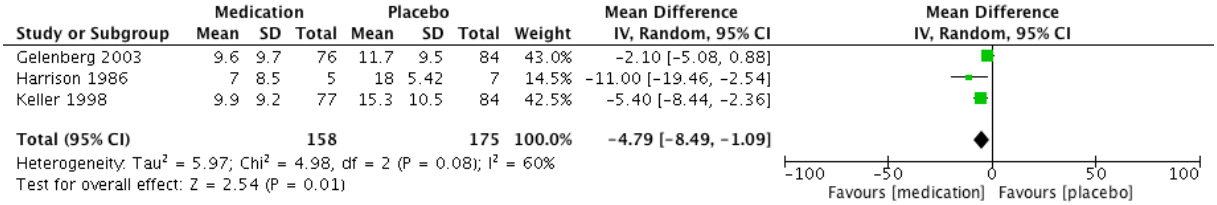

Figure 10. Forest plot of comparison: Medication versus placebo, outcome: Depression severity.

One RCT (Keller 1998) provided quality of life measures at end of intervention and reported three subscales of the SF-36. In this maintenance treatment study, participants in the medication arm reported both higher social functioning (MD = 10.80, 95% CI = 3.04 to 18.56; participants = 161) and less limitations owing to emotional problems (MD = 20.70, 95% CI = 7.43 to 33.97; participants = 161). No significant difference was found for the subscale of role limitations owing to physical health problems. Three RCTs provided data on dropout due to adverse events at end of intervention and indicated no significant difference between medication and placebo (figure 11). Two of them were maintenance treatment studies (Gelenberg 2003; Keller 1998), while Harrison 1986 was a continuation treatment study.

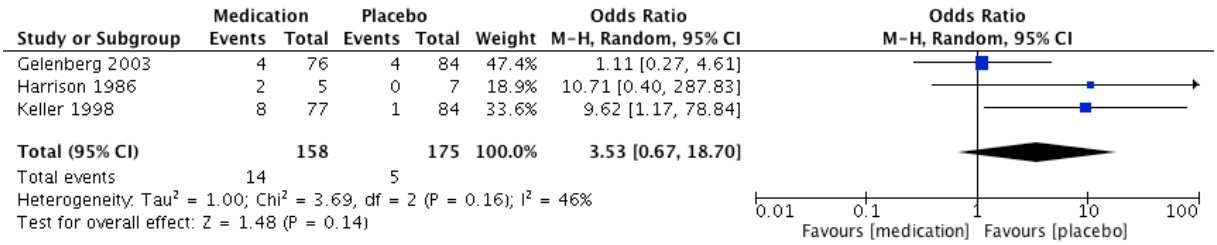

Figure 11. Forest plot of comparison: Medication versus placebo, outcome: Dropout due to adverse event.

One RCT (Keller 1998) provided data on experiencing any adverse event (physical problems like headache or insomnia) at end of intervention. In this maintenance treatment study no significant difference between medication and placebo were found (OR = 1.47, 95% CI = 0.70 to 3.09; participants = 161). The continuation treatment study of Harrison 1986 (RCT) also provided data on adverse events, but solely for the medication group. In the medication group all participants suffered from adverse events.

No data on serious adverse events available.

2 Pharmacological continuation and maintenance therapies versus treatment as usual (TAU). None of the included studies provided data on this comparison.

3 Psychological continuation and maintenance therapies versus attention placebo/nonspecific control

One maintenance treatment study (RCT) provided data on the comparison psychotherapy versus assessment only (Klein 2004, N = 82).

Primary outcomes

Rates of relapse/recurrence were significantly lower in the psychotherapy arm (RR = 0.37, 95% CI 0.14 to 0.93; participants = 82). This translates to a NNTB of five.

There were no significant differences between the overall dropout rates of the two groups (RR = 0.87, 95% CI = 0.41 to 1.81; participants = 82).

Secondary outcomes

The depression severity was significantly lower in the psychotherapy group at end of intervention (MD = -4.00, 95% CI = -7.05 to -0.95; participants = 82).

No data on quality of life available. No data on dropout due to adverse events available. No data on experiencing any adverse events available. No data on serious adverse events available.

4 Psychological continuation and maintenance therapies versus treatment as usual (TAU). None of the included studies provided data on this comparison.

5 Psychological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies

One continuation treatment study (Kocsis 2003, N = 179) provided data on the comparison psychotherapy versus medication, applying a non-randomized controlled trial (NRCT).

Primary outcomes

Concerning relapse/recurrence rates, there were no significant differences between the two treatment arms (RR = 1.22, 95% CI = 0.43 to 3.49; participants = 176). There were no significant differences in dropout rates between the two treatment arms, although a tendency favoring psychotherapeutic treatment is observable (RR = 0.56, 95% CI = 0.30 to 1.03; participants = 179).

Secondary outcomes

No data on depression severity scales available. No data on quality of life available. No data on dropout due to adverse events available. No data on experiencing any adverse events available. No data on serious adverse events available.

6 Combined psychological and pharmacological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies alone

Two continuation treatment studies provided data on this comparison: Kocsis 2003 (NRCT) compared nefazodone (N = 91) to nefazodone combined with CBASP (N = 150), while Hellerstein 2001 (RCT) compared fluoxetine only (N = 19) to a combination of fluoxetine and group psychotherapy (N = 20).

Primary outcomes

Kocsis 2003 (NRCT) provided data on relapse/recurrence rates, showing no significant difference between participants taking medication only (nefazodone) or medication combined with psychotherapy (CBASP) (RR = 1.23, 95% CI = 0.44 to 3.44; participants = 238). Both studies provided overall dropout rates at end of intervention and found no significant differences between medication only and the combined treatment. No heterogeneity was found between studies (RR = 1.43, 95% CI = 0.90 to 2.29; participants = 280; I^2 = 0%) (figure 12).

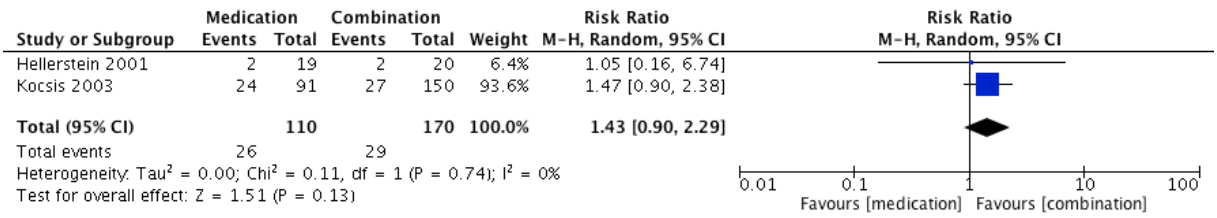

Figure 12. Forest plot of comparison: Medication versus combined treatment, outcome: Dropout any.

Secondary outcomes

Continuous data were available from the RCT of Hellerstein 2001. Participants in the combined treatment group showed a significantly lower symptom severity on the HAM-D at end of intervention compared to the medication only group (MD = 2.80, 95% CI = 0.38 to 5.22; participants = 39). This study also provided follow-up data 12 weeks after the end of intervention. No significant differences between both treatment conditions were found (MD = 0.90, 95% CI = -3.26 to 5.06; participants = 39). Hellerstein 2001 (RCT) provided quality of life measures at end of intervention (MD = -0.50, 95% CI = -1.63 to 0.63; participants = 35) and at follow-up 12 weeks after end of intervention (MD = 0.60, 95% CI = -0.56 to 1.76; participants = 33), using the Satisfaction with Life Scale (SWLS). There were no significant differences between both treatment conditions at either time point. No data on dropout due to adverse events available. No data on experiencing any adverse events available. No data on serious adverse events available.

7 Combined psychological and pharmacological continuation and maintenance therapies versus psychotherapeutic continuation and maintenance therapies alone

One continuation treatment study (Kocsis 2003) provided data on the comparison psychotherapy (CBASP, N = 88) versus combined treatment (nefazodone + CBASP, N = 150), applying a non-randomized controlled trial (NRCT).

Primary outcomes

Rates of relapse/recurrence did not differ between participants receiving psychotherapy alone or in combination with medication (RR = 1.51, 95% CI = 0.57 to 4.01; participants = 234).

Overall dropout rates at end of intervention did not differ between both treatment conditions (RR = 0.82, 95% CI = 0.45 to 1.51; participants = 238).

Secondary outcomes

No data on depression severity scales available. No data on quality of life available. No data on dropout due to adverse events available. No data on experiencing any adverse events available. No data on serious adverse events available.

8 Comparison of different antidepressant medications (post hoc analyses)

Two continuation treatment studies (both NRCTs) provided data on the comparison of two different antidepressant medications (Kocsis 1995; Koran 2001). Although we did not predefine this comparison as a main comparison of interest in the study protocol, we will report this additional data.

8.1 Imipramine versus Desipramine

One study (Kocsis 1995, N = 73) provided data on the comparison of two different tricyclic antidepressants (imipramine and desipramine).

Primary outcomes

8.1.1 Relapse/recurrence rates of depression

No data on relapse/recurrence rates of depression available. Significantly more participants dropped out in the imipramine group (RR = 4.35, 95% CI = 1.19 to 15.87; participants = 73). This translates to a NNTB of five, that is, five participants must be treated with desipramine in order to maintain one additional participant in treatment.

Secondary outcomes

No data on depression severity scales available. No data on quality of life available. There were no significant differences between the dropout rates due to adverse events of the two groups (RR = 1.45, 95% CI = 0.26 to 8.09; participants = 73). No data on experiencing any adverse events available. No data on serious adverse events available.

8.2 Imipramine versus Sertraline

One study (Koran 2001, N = 386) compared a tricyclic antidepressant (imipramine) with a selective serotonine reuptake inhibitor (sertraline).

Primary outcomes

No significant differences between the relapse/recurrence rates of the two treatment arms occurred (RR = 1.27, 95% CI = 0.84 to 1.91; participants = 376). There were no significant differences between the overall dropout rates of the two groups (RR = 0.81, 95% CI = 0.48 to 1.38; participants = 386).

Secondary outcomes

The depression severity (measured with the HAM-D) at end of intervention did not differ significantly between imipramine and sertraline (MD = 0.40, 95% CI = -0.97 to 1.77; participants = 377). The degree of enjoyment and satisfaction in different areas of daily functioning (Q-LES-Q) at end of intervention was significantly higher in the sertraline group (MD = -4.30, 95% CI = -7.31 to -1.29; participants = 347). There were no significant differences between the dropout rates due to adverse events of the two groups (OR 1.99, 95% CI 0.60 to 6.65; participants = 386).

8.2.6 Experiencing any adverse event

No data on experiencing any adverse events available. No data on serious adverse events available.

Subgroup analyses

We were not able to perform any of the a priori defined subgroup or meta-regression analyses due to limited number of studies.

Sensitivity Analyses

We could perform sensitivity analyses only for one comparison (pharmacological continuation and maintenance therapies versus placebo) as all other comparisons did not provide enough data.

Excluding studies with a high or unclear risk of bias

For each risk of bias domain, we planned to exclude the studies with high or unclear risk to compare these results with the results of the analysis including all studies.
For the domains *'random sequence generation'*, *'allocation concealment'*, and *'selective reporting'*, none of the studies had a low risk of bias, thus these sensitivity analyses could not be performed. Concerning the domain *'blinding of participants and personnel'*, all of these studies had a low risk of bias. With regard to the domain *'blinding of outcome assessment'*, only the study of Gelenberg 2003 had a low risk of bias. When including only Gelenberg 2003, the difference between medication and placebo concerning 'relapse/recurrence' did not reach significance (RR = 0.76, 95% CI 0.47 to 1.23, p = 0.27), whereas concerning 'dropout any', there appeared a significant difference (RR = 0.48, 95% CI 0.24 to 0.94, p = 0.03) favouring medication. With regard to 'depression severity' the difference between medication and placebo missed significance (MD = -2.10, 95% CI -5.08 to 0.88, p = 0.17) when including Gelenberg 2003 only. Referring to 'dropout due to adverse event', there was no significant difference between medication and placebo – consistent with the original results.

Concerning the domain '*incomplete outcome data'*, we excluded the study of Keller 1998 as it had a high risk in this domain. There was no change concerning the findings on the outcome measures 'relapse/recurrence' and 'dropout any' (except a lower rate of heterogeneity in the latter). Concerning 'depression severity', the heterogeneity increased when excluding Keller 1998. Medication was still superior to placebo but the differences between the two groups missed significance (MD = -5.63, 95% CI -14.17 to 2.90, p = 0.20).

Concerning 'dropout due to adverse event' the results did not change substantially when excluding Keller 1998.

Regarding the domain *'Other potential sources of bias'*, the studies of Kocsis 1996 and Miller 2001 (comparing desipramine with placebo) with the partially overlapping subgroup had a low risk of bias. Including only Kocsis 1996, the difference between medication and placebo regarding 'relapse/recurrence' remained significant. Regarding 'dropout any' the difference between medication and placebo missed significance – corresponding to the original results. Concerning 'depression severity' and 'dropout due to adverse event' there were no data available for Kocsis 1996.

Summarizing, the sensitivity analyses could only focus on three of the seven risk of bias domains and on the two primary outcomes (relapse/recurrence, dropout any) and on two secondary outcomes (depression severity, dropout due to adverse event).

Exluding trials without a randomization on a personal level or without (re-)randomization before the continuation phase

We could not perform these analyses as all studies providing data on the comparison pharmacological continuation and maintenance therapies versus placebo were RCTs with randomization on a personal level.

Post hoc sensitivity analyses

As there were two partially overlapping groups included (Kocsis 1996 and Miller 2001) in our review regarding the comparison pharmacological continuation and maintenance therapies versus placebo, we decided to perform an a posteriori defined sensitivity analysis (including Miller 2001 instead of Kocsis 1996). Miller 2001 investigated the dysthymic subsample of Kocsis 1996 but also included additional dysthymic subjects. Miller 2001 only provided data on the outcome 'relapse/recurrence'. The risk ratio was slightly lower (RR = 0.38, 95% CI 0.16 to 0.89) with a broader confidence interval and a slightly higher

heterogeneity (I^2 = 58%) when including Miller 2001 instead of Kocsis 1996. We consider these differences as clinically not meaningful (figure 13).

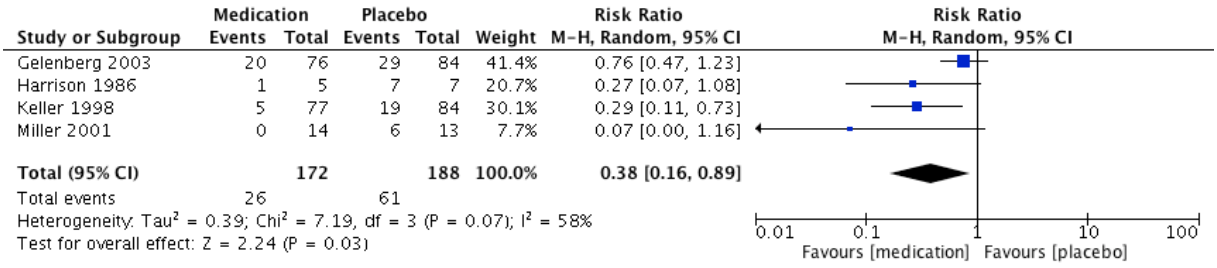

Figure 13. Forest plot of comparison: Pharmacological continuation and maintenance therapies versus placebo, outcome: Relapse/recurrence. Sensitivity Analysis.

4.1.6 Discussion

Summary of main results

This review is based on data from 10 studies, from which five studies investigated continuation treatments and five studies investigated maintenance treatments. All maintenance treatment studies and two continuations treatment studies applied a randomized-controlled design (RCT). The remaining three continuation treatment studies used a non-randomized-controlled design (NRCT). Five studies included comparisons of antidepressant medication versus pill placebo. Only three studies involved psychological treatment. Two of these three studies investigated the effect of CBASP (compared to antidepressant medication or their combination), or against assessment only, while the other study compared antidepressant medication with a combination of medication and group therapy. We also analyzed data for an a posteriori defined comparison as data of two studies were available, namely the direct comparison of two antidepressant medications. All 10 studies reported data at end of intervention, while only one study also reported follow-up data 12 weeks after end of intervention.

Pharmacological continuation and maintenance therapies versus placebo

Five studies compared continuation or maintenance antidepressant medication with pill placebo. The class of antidepressant medication varied between the included studies, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, serotonin-norepinephrine-dopamine reuptake inhibitors and tricyclic antidepressants were used. For the analyses, we excluded one study (Miller 2001) due to an overlapping group of patients with the study of Kocsis 1996. Our analysis based on four studies involving 383 participants revealed that participants taking antidepressant medication had significant less relapses or recurrences and a lower depressive symptom severity score compared to participants taking placebo at end of intervention. The results did not change significantly when replacing Kocsis 1996 by Miller 2001.

Continuation/maintenance antidepressant medication reduced risk of *relapse/recurrence* with an NNTB of six. Heterogeneity between studies was moderate. For the outcome *relapse/recurrence*, three studies (Keller 1998; Harrison 1986; Kocsis 1996) showed similar between-group effect sizes, although these studies varied largely regarding treatment duration and sample size. In comparison, in Gelenberg 2003, the effect favoring medication was smaller with a rather narrow CI. Miller 2001 showed a very strong effect favoring medication with a very large CI (due to small sample size). In the latter, solely dysthymic participants were treated over a period of 104 weeks, therefore the design and setting of this study is different from the other four studies. Besides, all studies used different antidepressants from varying classes, which could have been contributed to the moderate degree of heterogeneity.

We found no significant differences between medication and placebo concerning the *overall dropout rate*. Heterogeneity was substantial ($I^2 = 64\%$). In Harrison 1986 no participant in the placebo group dropped out, but they reported that all participants in the placebo group relapsed (therefore a dropout due to other reasons than relapse/recurrence was

not possible by definition). Besides, two studies (Harrison 1986; Kocsis 1996) investigated rather small sample sizes, resulting in large CIs.

Participants taking antidepressant medication had a significantly lower *depressive symptom severity score* compared to participants taking placebo at end of intervention (based on three RCTs). Two of these studies, both maintenance treatment studies (Keller 1998 and Gelenberg 2003) showed very similar results, both in means and SDs pre- and posttreatment and generally, in design of the study (maintenance phase, lasting 76 or 52 weeks, respectively). Treatment duration in the continuations treatment study of Harrison 1986 was 26 weeks, and participants in the medication arm reported lower and participants in the placebo group higher symptom severity scores compared to the corresponding groups in the other two studies. These factors might have contributed to considerable heterogeneity between the three studies. Considering the results regarding *relapse/recurrence* and *depression symptom severity*, it can be assumed that continued and/or maintained pharmacotherapy is superior to pill placebo in persistent depressed participants.

Three RCTs (Keller 1998; Harrison 1986; Gelenberg 2003) provided data *on dropout due to adverse event*s at end of intervention and indicated no significant difference between medication and placebo. These three studies varied in sample size, dropout rates due to adverse events in general and also between treatment arms, potentially contributing to the moderate degree of heterogeneity. In the continuation treatment study of Harrison 1986, no participant in the placebo group dropped out due to adverse events, but all of these participants relapsed (before), and this study had a small sample size and rather short treatment duration compared to the other two studies. The maintenance treatment study of Keller 1998 showed considerable differences in dropout rates between the treatment arms, favoring placebo, and treatment lasted 76 weeks. In comparison to the other two studies, Gelenberg 2003 showed the smallest difference in dropout rates due to an adverse event between the medication and placebo group during the maintenance treatment phase. It is

unclear if participants actually took the medication throughout the entire maintenance phase as no laboratory tests were reported. This could possibly lead to less reporting of adverse events. One study (Keller 1998) provided *quality of life* measures, in which participants in the medication group benefitted compared to placebo.

Sensitivity analyses predominantly revealed no relevant differences between original results and exclusion of all studies with high or unclear risk of bias in the single domains. There were two exceptions: Medication did not remain significantly superior to placebo concerning depression severity when excluding Keller 1998. When excluding all studies but Gelenberg 2003, the results changed with respect to relapse/recurrence and depression severity (the difference between medication and placebo missed significance) as well as overall dropout rate (there was a significantly lower dropout rate in the medication group). However, it remains unclear if these disparate results can be reduced to the potential risk of bias in the excluded studies or if they mainly can be explained by the specific study characteristics of Gelenberg 2003.

Psychological continuation and maintenance therapies versus attention placebo/nonspecific control

One maintenance treatment study with 52 weeks duration (Klein 2004), involving 82 participants, provided data on this comparison. The study showed less *relapses/recurrences* and a lower *depression severity score* in the CBASP group compared to the assessment only group at end of intervention. Maintained CBASP treatment reduced the risk of relapse/recurrence with a NNTB of five. *Overall dropout rates* were similar in both treatment arms. It might be assumed that maintained active psychotherapy has a positive effect on depression outcomes compared to assessment only.

Psychological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies

Only one study (Kocsis 2003) involving 179 participants provided data on the active comparison of psychotherapy with medication during the continuation treatment phase. Although participants receiving CBASP and those taking nefazodone did not differ regarding *relapse/recurrence* and *overall dropout rate* at end of intervention, a tendency favoring psychotherapeutic treatment was observable regarding dropout.

Combined psychological and pharmacological continuation and maintenance therapies versus pharmacological continuation and maintenance therapies alone

Three studies contributed data for this comparison. One continuation treatment study (Kocsis 2003) involving 238 participants provided *relapse/recurrence rates* and showed no statistical significant differences between the group taking nefazodone and the group receiving both CBASP and nefazodone. Two studies (Kocsis 2003; Hellerstein 2001) involving 280 participants provided *overall dropout rates*, showing no statistical significant differences between medication alone and the combined treatment. One study (Hellerstein 2001) involving 39 participants reported a significant lower *depression severity score* for the combined group compared to medication alone at end of intervention. However, this effect did not remain at the 12 week follow-up. This same study provided *quality of life* measures, but found no differences between both treatment groups at end of intervention and follow-up.

Combined psychological and pharmacological continuation and maintenance therapies versus psychotherapeutic continuation and maintenance therapies alone

One continuation treatment study (Kocsis 2003) involving 238 participants provided *relapse/recurrence* and *overall dropout rates* for this comparison and showed no significant differences between the CBASP group and participants receiving the combination of CBASP and nefazodone.

Comparison of different antidepressant medications (post hoc analyses)

Two studies reported data on the direct comparison of two antidepressants. One continuation treatment study (Kocsis 1995) involving 73 participants compared two tricyclic antidepressants, whereby *overall dropout rates* were higher in the imipramine group compared to the desipramine group. Compared to imipramine, desipramine reduced the dropout risk with a NNTB of five. *Dropout rates due to adverse events* did not differ significantly between the two groups. The imipramine sample was relatively small (N = 23) and only half the size of the desipramine sample. The three dropouts in the desipramine group dropped out due to dissatisfaction with treatment response or due to side effects. In the imipramine group, one participant discontinued because of side effects, one participant had a dispute with the staff and four participants did not comply with the follow-up assessment. Data on *relapse/recurrence* rates were not provided in this comparison.

The second study (Koran 2001), a continuation treatment study involving 386 participants, compared a tricyclic antidepressant with a selective serotonine reuptake inhibitor, showing no significant differences between treatment arms regarding *relapse/recurrence*, *overall dropout rate*, *dropout rate due to adverse events* and *depression severity* at end of intervention. This study provided *quality of life* measures, in which participants of the SSRI group reported a significant higher quality of life at end of intervention.

Overall completeness and applicability of evidence

Only 10 studies were identified for inclusion in this review. Most of the searched studies could not be included into the review as they treated either solely participants with recurrent depression (with clear interepisode remission and an episode duration shorter than two years), they did not clearly assess the percentage of diagnostic subgroups of persistent depressive disorder or no subgroup analyses were reported. Thus, it can be assumed that there

are more studies on hand involving persistent depressed participants, but as no specific percentages were available from the publications or following contact with the authors, this data could not be considered for this review. Moreover, some long-term studies had to be excluded because they did not define clear response or remission criteria for entering the next treatment phase which we required for inclusion into the review as response or remission are considered as accurate criteria of continuation or maintenance treatments [8]. Overall, this resulted in a rather small body of evidence available for addressing the objectives of this review.

Regarding the 10 included studies, for most comparisons only one or two studies provided data for the analyses, limiting the informative value of the presented results. For the comparison of antidepressant medication and placebo, five studies provided consistent data although different classes of medication were applied. Only three of the included studies involved psychological treatments, two of them applied in individual setting (CBASP), the other applied as a group therapy, both conducted in an outpatient setting in the US. More studies are required to evaluate the different forms of psychotherapy (e.g., Interpersonal Psychotherapy, Cognitive-Behavioral Therapy, CBASP, Mindfulness-Based Cognitive Therapy, Psychodynamic Therapy) in varying treatment settings (individual, group), cultures and health care systems. Moreover, just two studies investigated the combination of psychotherapy and antidepressant medication although guidelines already recommend the combined treatment for persistent depressive disorders [6]. Also, we expected to include comparisons with treatment as usual, investigating if long-lasting continuation and maintenance treatments are implemented in health care systems and evaluating these treatments under natural conditions. Unfortunately, no study using this comparator could be identified.

From the 10 included studies, five were continuation studies, five maintenance studies. Maintenance treatment studies varied largely regarding the duration of treatment (12 to 24

months), while the preceding continuation treatment studies were more similar in duration (16 to 20 weeks). Per definition, participants remitted or at least partially responded during acute treatment should start continuation treatment within one year after terminating acute treatment. Then, maintenance treatments should be given during recovery, which is defined as remission lasting longer than six months [8, 45]. Three studies providing a continuation treatment phase defined a duration of 16 to 20 weeks treatment before participants entered a subsequent maintenance phase. This does not correspond to the recommended criterion of six months recovery before entering maintenance treatment. Still, we decided to include these studies into the review and followed the definition of the authors as they described reasonable criteria for participants being eligible entering the maintenance phase. We kept the term "maintenance treatment" for these treatments as they were longer than the examined continuation treatments, consistently. Due to the small amount of included studies we did not differentiate between effects of continuation versus maintenance treatments during the analyses, which would be valuable considering the distinct criteria of remission/recovery for both treatment phases. Especially in persistent depressive disorder with participants showing severe levels and duration of symptoms, clear criteria for receiving both treatments following acute therapy are required. Therefore, a consistent application of the terms continuation and maintenance treatment and corresponding implementation into research and health care is needed before definite conclusions about the effectiveness of such treatments can be drawn.

For this review, the primary efficacy outcome was relapse or recurrence. Most of the studies applied rather strict criteria for participants to fulfil this outcome criterion at end of intervention, e.g., exceeding cut-offs during two or three consecutive sessions followed by a personal interview with a study investigator clarifying a potential diagnosis. Such procedures contribute to keeping participants longer in the study program and possibly underestimate absolute relapse and recurrence rates. Different definitions of this outcome between the included studies also prevent a comparison of absolute relapse/recurrence rates between the

examined treatments. Additionally, it must be kept in mind that two different target figures were mixed here: Relapse defines the return of symptoms before full remission is reached, while recurrence indicates a new episode after a full remission has been reached.

The primary acceptance outcome was dropout due to any reason (other than relapse/recurrence), of which data were reported in nine of the 10 studies. Specific reasons for dropout were described rarely, instead more often side effects evolved in at least 10% of participants were mentioned. But, next to side effects, also other negative events as interpersonal problems (e.g., conflicts with others) might occur during or after treatment. Such adverse events were reported very rarely in the included studies of this review, but should be addressed clearly in future research [59]. Especially in long-term treatments as continuation and maintenance treatments, dropout is considered likely and should be assessed in more detail (e.g., if participants dropped out due to aspects of the intervention itself or due to other reasons).

Another secondary outcome of interest of this review were quality of life measures. Only three of the 10 studies address this outcome although psychotherapeutic and pharmacological treatments are considered to improve quality of life in depressive disorders [163]. As persistent depressive disorders are characterized by a chronic course, an exclusive focus on improvement of depressive symptomatology over a long time might be too narrow to describe health status of participants completely. Including quality of life measures more frequently into studies is recommended.

Moreover, we intended to analyze data at the time point ‘one year after the end of intervention’. Surprisingly, just one of the 10 studies provided follow-up data, and even this study addressed a short follow-up duration (12 weeks). Especially in persistent depressive disorder we consider the evaluation of long-term effects beyond termination of treatment as highly relevant and valuable information to provide recommendations on when therapy should be extended, changed or terminated.

Another aspect regarding the applicability of evidence is date of publication. Studies included in this review were published between 1986 and 2004. The current practice including available medication and psychotherapy for treating patients with persistent forms of depression might have been different at that time. For example, the drug nefazodone used in two of the included studies (Kocsis 2003; Gelenberg 2003) was withdrawn from the market in 2003 respectively 2004 in some countries due to the rare incidence of hepatoxicity [74].

Quality of the evidence

For most of the planned comparisons only one or two studies provided data. Thus, we report a summary of findings table only for the comparison of pharmacological continuation and maintenance therapies versus placebo, referring to the quality of evidence of the primary outcomes relapse/recurrence and overall dropout (see table 2).

Limitations in study design or execution (risk of bias)

We included seven randomized controlled trials (RCTs) and three non-randomized controlled trials (NRCTs) involving 840 participants with persistent depressive disorder. Two of the three NRCTs were evaluated as having almost no risk of bias in the seven domains, while the other study was classified between moderate and serious risk for more than half of the domains. The seven included RCTs varied regarding risk of bias domains, and were rated mostly as low or unclear risk of bias, with one exception. One study (Hellerstein 2001) was rated as having a high risk of bias in four domains and unclear risk of bias in three domains.

Table 2 *Summary of findings table*

Pharmacological continuation and maintenance treatment compared with placebo for persistent depressive disorder						
Patient or population: people with persistent depressive disorder Settings: outpatient treatment Intervention: pharmacological continuation or maintenance treatment (sertraline, phenelzine, nefazodone, desipramine) Comparison: pill placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	placebo	pharmacotherapy				
Relapse/recurrence (end of intervention)	**338 per 1000**	**139 per 1000**[1] (71 to 267)	**RR 0.41** (0.21 to 0.79)	383 (4 studies)	⨁⨁⨁⨁ **high**	The criteria of relapse/recurrence are provided in the "characteristics of studies"-tables of each included study.
Dropout any (end of intervention)	**255 per 1000**	**230 per 1000**[1] (99 to 538)	**RR 0.90** (0.39 to 2.11)	386 (4 studies)	⨁⨁◯◯[2, 3] **low**	"Dropout any" is defined as all reported dropouts due to other reasons than relapse/recurrence. One study (Kocsis 1996) only reports dropouts in the first month of the maintenance treatment phase. As the maintenance treatment lasts 24 months, the dropout rate in this study is very likely to be underestimated.
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio						
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.						

[1] *assumed risk calculated as the proportion of participants on placebo with the outcome (relapse/recurrence or dropout any) in the four included studies, multiplied by 1000.*
[2] *downgraded due to unexplained heterogeneity between studies (I^2=64%). Due to the small number of included studies, subgroup or meta-regression analyses were not performed. In two studies, dropout rates were higher in the intervention group, in two studies they were lower.*
[3] *downgraded due to imprecision of results (the overall confidence interval is wide and the confidence intervals of two included studies are also very wide).*

In general, allocation concealment and random sequence generation was addressed in none of the studies and therefore rated as unclear risk, and selective reporting was rated as unclear risk in five of these seven studies. One study (Kocsis 1996) with high risk of bias in the domain selective reporting analyzed data on dropout during the 104 week maintenance phase, but only the rates during the first month of treatment, probably underestimating the actual dropout rate over time.

To separate the two primary outcomes (relapse/recurrence and overall dropout), we did not include the participants with relapse/recurrence in the overall dropout rates. This must be kept in mind when interpreting the absolute dropout rates. Additionally, as in one study (Harrison 1986) all participants in the placebo group relapsed and there is no information on the time of relapse, the dropout rate in this group is zero, possibly overestimating the acceptance of this treatment. If the participants relapsed early, there was „no chance“ for accepting or not-accepting the treatment. Incomplete outcome data was rated as high risk in two studies (Hellerstein 2001, Keller 1998) as they applied the Last Observation Carried Forward (LOCF) method for imputing missing values. In Keller 1998, 70% of the participants in the placebo group dropped out during the 76 week maintenance treatment, thus the missing data were replaced by the last available measure of the participant. Although this method is commonly used for analyzing longitudinal data, we consider this procedure inappropriate within the context of continuation/maintenance treatments as it potentially underestimates relapse and recurrence rates. As LOCF assumes that the missing data after the participant's dropout stay the same as the last value observed for that participant [164], we assume that LOCF provides rather optimistic estimates instead of conservative estimates. This assumption of stability is rather unlikely for persistent depressive disorder over long periods of time considering the high likelihood of recurrences reported in previous research.

Analyses regarding dropout rates for the comparison of antidepressant medication versus placebo resulted in serious heterogeneity between studies. Due to the small amount of studies we were not able to analyze these differences statistically.

These circumstances in combination with the mentioned limitations of the studies contributed to downgrading the body of evidence for this comparison regarding the outcome dropout (other than relapse/recurrence) to low (see table 2, p. 97). However, for the comparison of relapse/recurrence rates in continued and maintained pharmacotherapy versus placebo treatment, four studies provided coherent data that involved 383 participants. The limitations in these studies were classified as existing but unlikely to produce significant change in effects, resulting in a rating of high quality of evidence (see table 2, p. 97). Consequently, we assume that persistent depressed participants benefit from long-lasting medication compared to pill placebo.

Inconsistency of results

Data were inconsistent in regard to overall dropout rates. Dropout rates varied between studies from 4% (Kocsis 1996) and 100% (Harrison 1986). This unexplained heterogeneity contributed to downgrading the quality of evidence to low regarding overall dropout rates in the comparison of antidepressant medication versus placebo.

Indirectness of evidence

All included studies directly addressed the objective of this review, namely the comparative effectiveness of continuation and maintenance treatments for persistent depressive disorder.

Imprecision of results

Two of four studies addressing overall dropout rates in the comparison of antidepressant medication versus placebo showed wide confidence intervals (Harrison 1986; Kocsis 1996). This contributed to downgrading the quality of evidence to low.

Publication bias

Due to the small numbers of included studies, funnel plots were only applied for the comparison antidepressant medication versus pill placebo. Apparently, the funnel plot on relapse/recurrence seems asymmetrical (figure 14), with an overhang of small studies showing a large difference in favor of medication), while the funnel plot on dropout is symmetrical (figure 15). The application of statistical tests (e.g., Egger's test) for funnel plot asymmetry was not conducted, as it is not advisable due to the small number of studies. The Cochrane Handbook [153] recommends these tests when there are at least 10 studies, otherwise the power is too low.

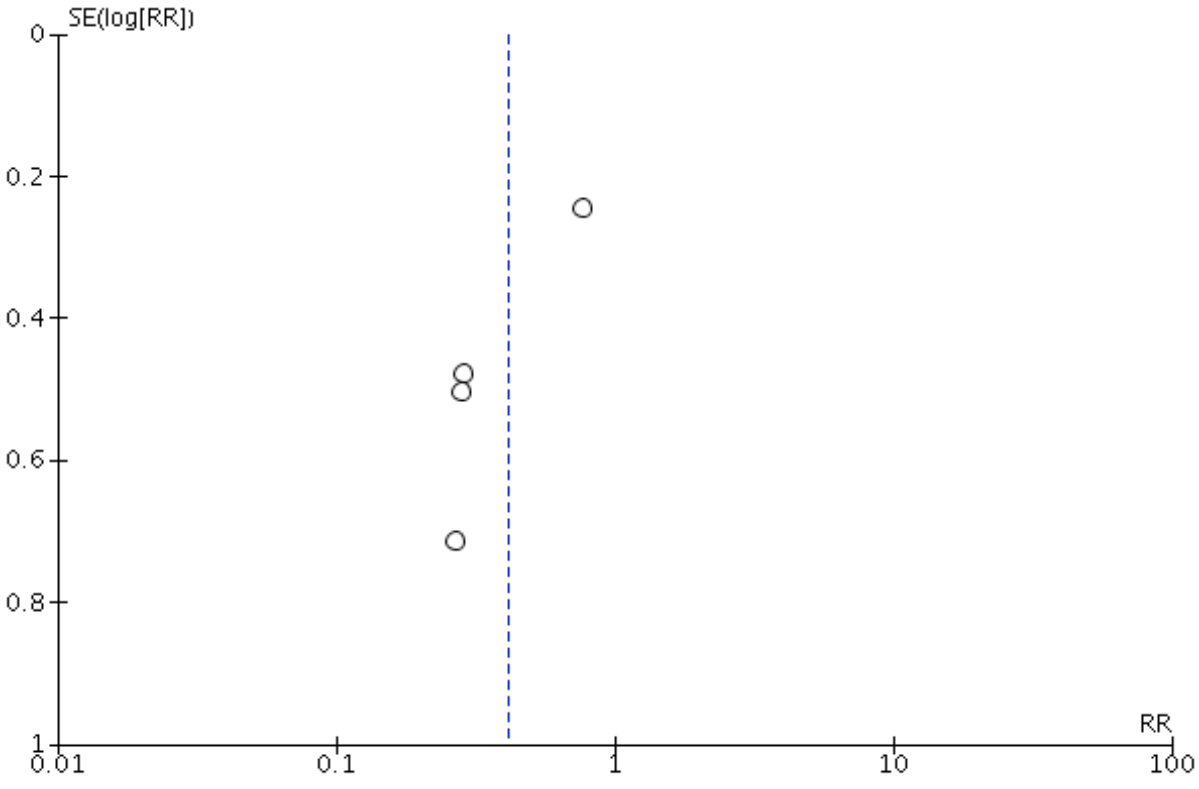

Figure 14. Funnel plot of comparison: Medication versus placebo, outcome: Relapse/recurrence.

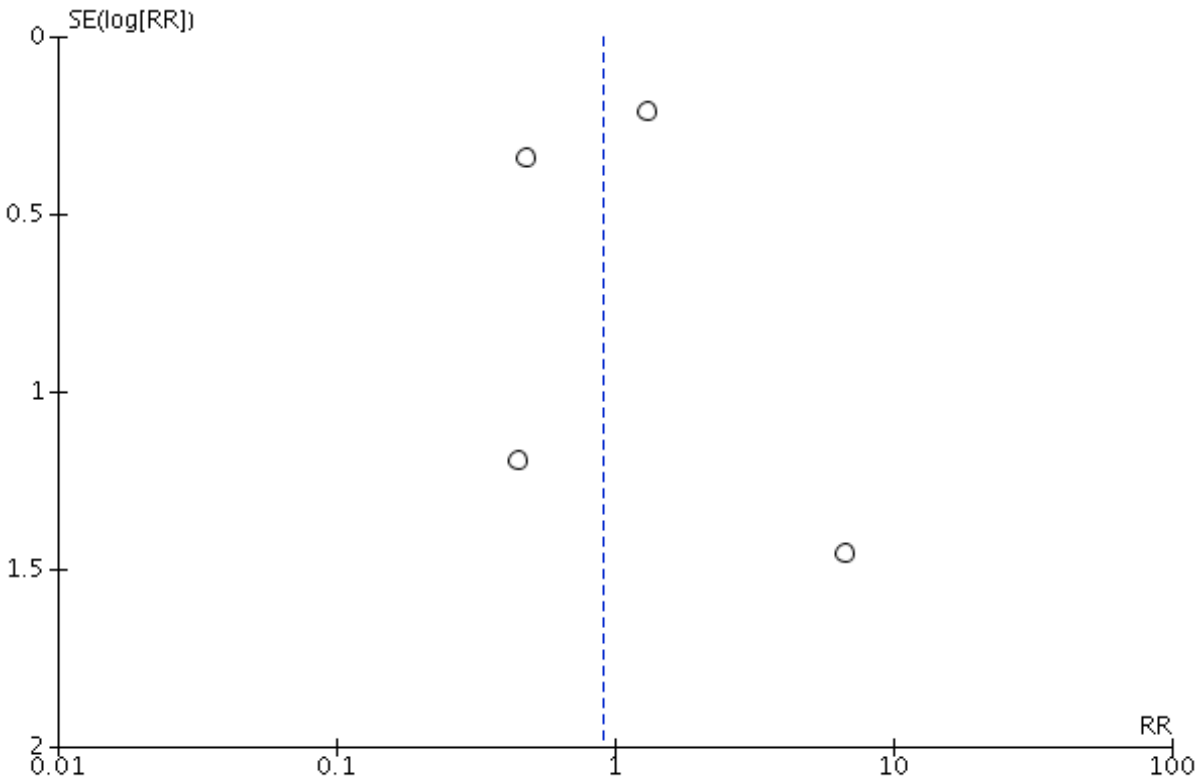

Figure 15. Funnel plot of comparison: Medication versus placebo, outcome: Dropout any.

Potential biases in the review process

We used a broad search strategy for identifying all relevant studies regarding continuation and maintenance treatments in persistent depressive disorder (PDD). The main search was conducted in the specialized register of randomized controlled trials of the Cochrane Common Mental Disorders Group (CCMD-CTR) searching for study and reference records. Moreover, we searched other databases, grey literature, clinical trials register and contacted relevant authors in this field. We had to exclude a considerable amount of studies as most studies either did not include specifically participants with PDD or did not report the percentage of treated PDD participants. Although we were in email contact with the first authors of the included papers regarding this missing information, they either did not reply to our queries or simply had specific data no longer available due to conducting these studies a long time ago. Therefore, we assume that more studies than included in this review were

conducted with participants with PDD. But these studies did not solely (more than 80%) treat participants, which PDD and therefore did not meet our inclusion criteria. Screening of records, extracting and analyzing data was conducted by at least two review authors independently to prevent any severe bias in the used methods.

However, there was marked clinical heterogeneity between the included studies, especially regarding sample size, subtype of persistent depression, kind of treatment (e.g., type of antidepressant medication), treatment duration and definition of relevant outcomes. Therefore, we are not reporting on a homogenous group of participants, manifesting in both studies investigating a specific subgroup (e.g., solely dysthymic participants) and studies investigating all four diagnostic subgroups of PDD, making it difficult to generalize the found results to PDD in general. This also applies to the type of treatment: Continuation and maintenance treatment with lengths between 16 weeks and two years were included, which allows no conclusion on continuation or maintenance treatment in general.

Also, PDD is a rather severe form of depression with patients probably suffering from comorbid disorders, suicidality or psychotic symptoms, and who usually underwent several other treatments before entering a study, which in turn was an exclusion criterion in some of the included studies for this review. Such excluded participants are probably in more need of high quality treatment but without receiving it, especially regarding continued and maintained treatment. This raises the question what kind of participants joined the studies we included for this review – severe impaired ones or less impaired ones? We required the included studies to report on ICD or DSM diagnosis of PDD, neglecting total duration of illness or other potential indicators of impairment. But, as we required clear response or remission criteria for considering continuation or maintenance treatment studies for this review, symptom level of included participants is considered rather homogenous. Some of the included studies were funded by grants of pharmaceutical industry. Conducting long-term continuation and maintenance studies requires considerable financial support, potentially leading to bias of the

found results if covered by third parties. However, we considered risk of publication bias as low but the application of a statistical test was not advisable due to the small number of studies. Additionally, the required length of treatment – especially of maintenance studies – is possibly one reason for the lack of studies in this field.

Another aspect of potential bias is the allowance or proscribing of concomitant treatments in addition to the treatment provided by the study. Two of the included studies investigating antidepressant medication reported that participants received ongoing psychotherapy. One study (Koran 2001) reported that 60% of the participants received ongoing psychotherapy while treated with sertraline or imipramine, yet no group differences were reported. In two studies, about 40% of the participants of both treatment groups (desipramine, placebo) were in stable long-term psychotherapy (Kocsis 1996, Miller 2001). Although parallel treatment is not necessarily considered biasing the results, especially when proportions are similar between treatment groups, the observed individual change is not solely based on study treatment but also on parallel treatment in the respective two studies. However, the other studies did not mention any information about parallel treatments or explicitly stated that no concomitant treatment was allowed.

Despite the discussed conceptual and methodological concerns we consider conducting a meta-analysis appropriate, especially for the comparison of antidepressant medication versus pill placebo. Sensitivity analyses addressed differences in risk of bias between studies, although results did not change in the majority of cases. Heterogeneity was planned to be addressed through subgroup and meta-regression analyses but due to the little amount of studies included we were only able to discuss differences between studies on a descriptive level. In general, for the majority of comparisons we had to describe the results on basis of one single study, not being able to report pooled results.

This review used two primary outcomes, rate of relapse/recurrence and rate of overall dropout due to other reasons than relapse/recurrence. Most of the studies reported on both

outcomes separately. Still, there is open discussion if both outcomes overlap conceptually in continuation and maintenance treatment studies. For example, in Harrison 1986 all participants of the placebo group relapsed, resulting in zero dropouts reported during treatment as participants simply had "no chance" for dropping out due to relapsing before, possibly overestimating the acceptance of placebo treatment.

Continuation and maintenance treatment studies are usually performed as complex studies, i.e., studies with different treatment phases (acute, continuation and maintenance treatment). Criteria and procedures of transition from one into the next phase differed between studies: Some studies defined response, some remission as an eligibility criterion for the next phase, including different definitions of response and remission (see above). Some studies did not re-randomize participants when entering the new phase (especially concerning the transition from acute to continuation treatment). Other studies re-randomized responders from one treatment arm to a different treatment arm in the next phase, e.g., Klein 2004 randomized continuation phase responders of CBASP to CBASP or assessment only in the maintenance phase. These different procedures complicate the comparability between different studies. Moreover, studies mostly described different treatment phases, resulting in partly overlapping patient groups included in different analyses.

As persistent depression is a chronic condition, relapses or recurrences are common in this population. Longer treatment durations (i.e., longer observation periods) probably increase the chance to observe relapses or recurrences, this must be kept in mind when comparing the results of different studies with varying treatment durations.

Concerning data analysis, there is no widely accepted consensus on how to deal with missing data in meta-analysis when primary data is not available. In acute phase studies, researchers can replace missing values with methods like last observation carried forward (LOCF), if study authors do not report adequate ITT-analyses. However, in the case of continuation and maintenance studies, we assume that LOCF would produce rather optimistic

instead of conservative estimates (see above) due to its concept of stability of measures over time [164]. Thus, we had to deal with the available data sets. However, percentages of missing data were low: Data on overall dropout rates were complete, the percentage of missing data concerning other outcomes ranged between zero and 10%.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first review evaluating the effectiveness of continuation and maintenance treatments in participants with persistent depressive disorder (PDD). A previous review investigated the efficacy and acceptability of acute treatments in PDD by applying network meta-analytic methods, showing that several antidepressant medications were superior to placebo, and that several evidence-based treatments exist [56]. Due to the small number of included studies in our review, comparisons between different antidepressants could not systematically be investigated. In line with the review of von Wolff and colleagues [58] on acute treatment in persistent depression, our review could also not provide a clear superiority of combined treatments compared to pharmacological monotherapy.

Regarding continuation and maintenance studies, Wilkinson and Izmeth [165] evaluated treatments for older people with depressive disorders. This updated Cochrane review identified seven studies of which six compared continued or maintained antidepressant medication with placebo, favoring antidepressants regarding relapse/recurrence at 12 months, but showing no significant differences between treatment arms at six or 24 months follow-up. Although this result is in line with our result for this comparison and outcome, Wilkinson downgraded the level of evidence to low (GRADE) compared to the GRADE rating of high level evidence in our review. Like in our review, Wilkinson and Izmeth [165] included just two studies involving psychological treatment, and data reported on this as well as combined treatments were too little to draw conclusions.

Regarding long-term effects of psychological treatments, Vittengl and colleagues [12] conducted a meta-analysis on effects of acute and continued cognitive–behavioral therapies (CT) in depression. They found high relapse and recurrence rates (29% within 1 year and 54% within 2 years) for participants discontinuing after acute CT. Those participants continuing CT had significantly less relapses and recurrences compared to active controls (e.g., receiving pharmacotherapy) at follow-up (10 to 255 weeks after end of continuation-phase treatment), with relapse/recurrence rates of 42% (continued CT) and 61% (active controls) over 114 weeks on average. In comparison, rates of relapse/recurrence were similar at end of (20 to 52 weeks) continuation phase for both CT and other active treatments, with relapse/recurrence rates of 10% (continued CT) and 22% (active controls) over 27 weeks on average. Although the results of Vittengl and colleagues [12] are encouraging to consider continued pharmaco- and/or psychotherapy in depression treatment, the analyses were based on only five to eight studies.

Guidi and colleagues [166] conducted a meta-analysis on the sequential integration of pharmacotherapy and psychotherapy in major depressive disorder, i.e., participants received pharmacotherapy in the acute phase and psychotherapy in the residual phase. Receiving CBT during continuation of antidepressant drugs was superior to antidepressants alone or treatment as usual. Further, participants receiving CBT who had medication tapered and discontinued were significantly less likely to relapse compared to clinical management or continued pharmacotherapy. These analyses were based on 13 studies.

Authors' conclusions

Implications for practice

This review comprises 10 studies and summarizes the current evidence of the effectiveness of continuation and maintenance treatments in persistent depressive disorder

(PDD). The comparison of antidepressant medication versus placebo showed coherent results based on five studies favoring pharmacotherapy as an effective continuation and maintenance treatment for participants with PDD compared to pill placebo regarding relapse/recurrence. On this basis, it can be concluded that continued and/or maintained pharmacotherapy with the reviewed antidepressant agents is a considerable treatment for preventing relapse and recurrence in patients suffering from PDD. As long-term follow-up data were not available in most of the studies, this review cannot draw any conclusions about an appropriate duration of antidepressant medication intake, or when to taper off or stop medication. In four of the five studies providing data on the comparison of medication versus pill placebo, medication in the placebo group was tapered down following an a priori defined scheme when starting a new treatment phase. Tapering down medication was predominantly used in the studies of this review, and is likely to be applied also in clinical practice instead of suddenly stopping medication.

Moreover, in two of the five studies reporting a benefit from antidepressant medication compared to placebo about half of the sample size had ongoing psychotherapy next to study treatment. Thus, it is unclear if the individual course of the analyzed patients is only attributable to the medication provided by the study, or also to the parallel psychotherapy treatment. Additionally, interaction effects may occur: 1) The effect of antidepressant medication could be underestimated because the received psychotherapy makes an additional treatment (antidepressant medication) less meaningful or 2) receiving parallel psychotherapy itensifies the effect of medication or keeps the participant motivated to stay on medication. For all other planned comparisons the body of evidence with mostly just one or two studies providing data was too small to draw final conclusions about recommendations for other kinds of treatment. However, psychological treatments were addressed in four comparisons. The 52 week maintenance treatment study (RCT) of Klein 2004 found less relapses/recurrences and a lower level of depressive symptoms in participants receiving

CBASP compared to assessment only at end of treatment. Although just this one study addressed this comparison, we rated most of the domains as unclear or low risk of bias, indicating that psychotherapy in the maintenance phase is useful. One continuation treatment study (Kocsis 2003) found less dropouts in the group of participants receiving CBASP compared to participants receiving nefazodone. We evaluated the risk of bias of this NRCT as low, indicating that psychotherapy in the continuation phase might be better accepted by participants compared to medication. Both studies provided CBASP in the psychological treatment arm, it might be assumed that patients can benefit from this form of psychotherapy during the continuation and maintenance phase in clinical practice.

Two studies addressed combined treatments. Hellerstein 2001 found a lower level of depressive symptoms in participants receiving medication combined with group therapy during the continuation phase compared with medication alone. We rated this RCT in all domains either with unclear or high risk of bias, questioning the implication for clinical practice. Kocsis 2003 compared CBASP with the combined treatment (CBAPS + nefazodone) and found no differences during the continuation phase. We evaluated the risk of bias of this NRCT as low, indicating that both psychotherapy and medication in the continuation phase might be effective interventions.

For the type of antidepressant medication as well as distinct treatment options for specific patient populations (e.g. subtype of persistent depression) the reported data of the included studies was too small to draw final conclusions or recommendations. Even concerning the comparison of antidepressants versus placebo, meta-regression or subgroup analyses were not possible due to the small number of eligible studies. Also, all included studies were conducted in the US and were published between 1986 and 2004. Thus, differences between cultures and health care systems, as well as current developments regarding recommendations of clinical guidelines are not covered by the studies selected for

this review. Conclusions and recommendations of this review should be interpreted on this background.

Implications for research

The above mentioned lack of studies on continuation and maintenance treatments in patients with persistent depression emphasizes the need for further primary studies – especially on psychological and combined treatments. The results of Vittengl and colleagues [12] suggest that long-term psychotherapy is effective in depression in general, emphasizing the need for verification the transferability of these results for the population of persistent depressive patients. Further studies should also assess health related quality of life as well as adverse events. Lack of reporting (consistently) on adverse events is a common problem in studies on acute treatment of persistent depressive disorder, especially in psychotherapeutic studies [59]. Generally, psychotherapeutic studies often fail to report on adverse events [60, 61]. Additionally, further studies should address follow-up evaluations. Comparing continuing treatment to stopping treatment in the long run is necessary to draw conclusions on the recommendable duration of continuation and maintenance treatments.

This review suggests the need for standardization of some terms and procedures. To compare study results among each other, standardized use of the terms “continuation” and “maintenance” as well as consistent definitions of relapse and recurrence are required. Different definitions for the transfer from one into the next treatment phase prevented the inclusion of further studies into this review as some studies evaluating long-term treatments included all participants (not only responders) or a clear separation of different treatment phases was lacking. Nevertheless, this probably reflects the clinical practice as it is likely that there is often no clear distinction between long-term acute treatment on one side and continuation or maintenance treatment on the other side.

As there is broad evidence on depression treatments on the one hand and a lack of studies fulfilling the inclusion criteria of this review on the other hand, clear diagnostic procedures as well as clear reporting concerning the persistence of depressive symptoms is necessary. It is reasonable that several excluded studies also examined participants with persistent depressive disorder, which could have been analyzed here if data on this subgroup would have been reported. The lack of reporting on this specific diagnosis reflects the fact that chronic major depression and recurrent depression without full interepisode remission may be designated as "(recurrent) major depression" in DSM-IV and ICD-10, ignoring the persistence of depressive symptoms. However, the new category "persistent depressive disorder" implemented in DSM-5 (duration of at least two years) increases the likelihood of a precise diagnosis concerning persistent symptoms.

4.1.7 Included studies (full references)

* Indicates that this reference is the primary reference for the study.

Gelenberg 2003

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Hellerstein 2001

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Keller 1998

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Klein 2004

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Marin D B, Kocsis J H, Frances A J, Parides M. Desipramine for the treatment of "pure" dysthymia versus "double" depression. The American journal of psychiatry 1994;151(7):1079-80.

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4.2 Maintaining patients' outcomes following psychotherapy by a telephone-based continuation therapy in recurrent and persistent depression: a mixed methods exploratory pilot study[5]

4.2.1 Abstract

Background. Persistent and recurrent depression are associated with a high risk of relapse indicating need for continued treatment to sustain remission in the long-term, but it is assumed that most patients receive inadequate or even no treatment. Delivering psychotherapy by telephone is considered valuable to provide many patients with treatment due to its low-intensity character, by ensuring personal contact within a flexible frame regarding location and time. Aim of the present study was to assess the feasibility of a six-month telephone-based continuation therapy for patients who responded to previous acute treatment.

Methods. Semi-structured interviews with participants and therapists were analyzed using qualitative content analysis. Depressive symptoms, depression-self-management and therapeutic alliance were assessed throughout therapy and at six-month follow-up. Using a mixed-methods approach we combined qualitative and quantitative data to obtain in-depth understanding of the intervention's components.

Results. Medium telephone was accepted, but relevance of an initial face-to-face meeting was reported if participant and therapist were unfamiliar. Low level of depressive symptoms and effective coping strategies were considered core conditions which need to be ensured before entering continuation therapy. A clear treatment plan implemented throughout therapy and prioritizing of contents within each session was required due to limited sessions and longer intervals between sessions. If one session per month was provided, fifty minutes was the preferred length of sessions. Reported benefit of intervention was associated with depressive

[5] For a similar version of this chapter see [167].

symptomatology and perceived fit with the participant's needs and attitude towards content and format of continuation therapy. The intervention was perceived feasible and especially valuable in high risk patients to ensure continuous long-term monitoring and support.
Conclusions. Continued psychotherapy delivered over telephone is assumed feasible if several preconditions as level of residual symptoms, coping strategies and fit between patient's needs and intervention components are ensured. Based on results of this pilot study, a randomized controlled trial assessing the effectiveness of a telephone-based continuation therapy is ongoing to further contribute to long-term relapse prevention in high risk individuals.
Trial registration: The trial was registered at clinicaltrials.gov on January 14, 2015 (NCT02397850).

4.2.2 Background

A substantial part of patients with a depressive disorder have a chronic or recurrent course [168] leading to persistent personal suffering, psychosocial impairment and also growing health expenditures. Chronic forms of depression include four diagnostic subgroups (dysthymia, chronic major depression, recurrent major depression with incomplete remission between episodes, double depression) [35] and are combined into one diagnosis referred to as *persistent depressive disorder (PDD)* according to the revision in the DSM-5 [13]. Whilst PDD is characterized by an illness duration of at least two years with persistent symptoms, *recurrent depression with clear interepisode recovery* is classified as an episodic form of major depressive disorder (MDD), indicated by a minimum of two episodes of MDD, which are separated by at least two months of normal functioning. Both PDD and recurrent depression are associated with severe impairments as increased loss of physical wellbeing, more frequent suicide attempts, and less social, psychological and emotional functioning,

more hospitalizations, and longer treatment duration compared to non-chronic or non-recurrent forms of depression [1, 17, 36, 37].

As people suffering from PDD or recurrent depression are at high risk of relapse and recurrence even after successful pharmacological or psychological acute treatment [11, 38, 169], continuation treatments should be provided to sustain remission in the long-term [6, 45].

Whilst antidepressant medication (ADM) is often continued on the same dose leading to remission during the acute phase [6], psychotherapeutic continuation treatments are not considered a simple extension of acute therapy, but rather contain the consolidation of skills a patient acquired during acute treatment across daily routine situations [39]. Thus, continuation treatments should be only provided to patients who previously responded to or remitted during an acute treatment [8, 45], allowing a less frequent therapeutic setting, i.e., longer intervals between sessions are considered meaningful [6].

Whilst the majority of studies address acute treatments in PDD and recurrent depression [12, 42, 56], considerable fewer studies focus on the efficacy and effectiveness of continuation therapies. Continued ADM is assumed effective in reducing relapse and recurrence as long as ADM is taken [46, 62, 64, 68], and is associated with adverse events [9] and dropout rates up to 25% between acute and continuation treatment phase [68]. Although studies addressing psychological interventions are heterogeneous in regard to design, intervention, treatment duration, and quality, psychotherapy might have equal effects, a lower risk of side effects and better long-term effects regarding behavioral change compared to pharmacological treatments [10]. Thus, components of long-term psychotherapeutic interventions should be determined.

A variety of long-term relapse preventive interventions were already investigated, mostly in individuals with non-chronic forms of depression [38], and mostly in cognitive-behavioral therapies (CBT). The proposed mechanisms underlying patient's change is usually considered the same for both the acute and continuation phase. For instance, in CBT it is

assumed that change in negative content of beliefs might lead to reduced symptoms and prevention of relapse [170], and this change is expected to maintain or even improve with continued CBT [171]. Jarrett and colleagues provided recurrently depressed patients who responded to acute CBT with either continued CBT or assessment visits (symptom monitoring) [136]. Based on a treatment manual, patients received ten sessions of continued CBT over eight months which focused on maintaining skills acquired during acute therapy, anticipating critical situations, developing coping strategies and reviewing strategies to reduce symptoms, i.e., targeting prevention of relapse and recurrence and consolidation of skills [39]. Patients receiving continued CBT showed significantly less relapses and recurrences during treatment and follow-up compared to the control group, especially in higher risk patients [136]. This is in line with a meta-analysis showing that patients who continued CBT relapsed significantly less than patients without any active continuation treatment, at posttreatment and follow-up [12]. Although continued CBT did not differ from other active therapies (e.g., continued ADM) at posttreatment, it showed better outcomes (i.e., less relapses and recurrences) compared to other active treatments during two years of follow-up. Evidence regarding psychological interventions in PDD is low, which makes it difficult to draw definite conclusions on the effectiveness of continued psychotherapy in PDD, yet [122].

Limited evidence in this field leaves open question if continued psychotherapy is not provided by mental health care, or if patients with PDD and recurrent depression are less likely to enter such treatment. By terminating acute therapy, patients report on better functioning, and thus, health insurances are probably less willing to cover the costs for treatment of an already remitted patient, and moreover, the patient might be eager to live without any therapeutic help at this point. Thus, patient's symptom relief might hinder initiating and maintaining treatment, but also dissatisfaction with (previous) treatments might do [83]. Generally, dropout rates tend to vary between 30% and 50% in studies addressing individual psychotherapy [83], and were found to be around 25% in individual and group

CBT for unipolar depression in routine clinical practice [84]. Also time constraints were perceived as barriers to involve in psychotherapy, and predicted less attending of psychotherapy within a one-year follow-up [88]. As low level of mood, interest and energy are key symptoms of depression, the above mentioned challenges have to be taken into account when conceptualizing continuation treatments.

One opportunity to meet these challenges is considered in *low-intensity treatments*, which are associated with fewer financial expenses due to less intense treatment and innovative delivery options increasing access to and maintenance of treatment [93]. Such treatments might include less or even no direct therapeutic involvement (compared to face-to-face settings) by using technologies as internet or mobile devices, and might involve highly qualified mental health professionals (e.g., psychotherapists) or non-professions (e.g., peer supporters). In recent years, internet-based interventions became more popular due to rapidly progressing technical development, and is associated with less costs and shorter waiting times compared to traditional face-to-face settings [172]. Meta-analyses demonstrate that CBT provided over the internet (iCBT) is superior to control groups (waiting list, usual care) in reducing depressive symptoms [95, 96], and that iCBT seems to be equally effective to face-to-face CBT in reducing depressive symptoms [100–102]. Meta-analyses also demonstrate that guided internet interventions lead to greater symptom reduction and less dropouts compared to unguided interventions [98, 99]. However, for some patients visual and auditory cues, which are missing in internet-based interventions, might be relevant for developing a sound therapeutic relationship [109], which in turn might enhance treatment outcomes [173].

Thus, delivering psychotherapy by telephone might be another flexible and low-threshold approach to provide many patients with mental health care, due to its low-intensity character in terms of low costs, overcoming barriers and practicability in everyday life [110]. While a personal contact between patient and therapist is guaranteed, delivering telephone therapy is more suitable in terms of arranging time and place of therapy than traditional face-

to-face settings. Telephone therapy as a stand-alone treatment in depressive disorders has been investigated only within the field of acute depression so far, and is associated with reducing depressive symptoms compared to control groups [111], and shows comparable effectiveness (e.g., with regard to level of depressive symptoms) as well as lower dropout rates than face-to-face settings in CBT [112–114]. Moreover, therapeutic alliance in telephone-based CBT for acute depression was found to be not inferior to face-to-face CBT [115]. Studies also indicate a relative cost-effectiveness of telephone-based interventions, with 36% less costs per sessions compared to face-to-face settings [116].

Delivering telephone-based therapy for individuals affected by PDD or recurrent depression might be an opportunity to provide adequate continuation treatment, which has a low-threshold access, is cost-effective and flexible in location and time, and is potentially reducing risk of relapse and recurrence in the long run. Thus, we piloted a telephone-based continuation psychotherapy provided over a period of six months among patients at high risk of relapse who responded to acute therapy previously.

4.2.3 Methods

Aim and objectives

To assess feasibility and acceptance of a low-intensity telephone-based continuation treatment after successful termination of acute therapy in individuals with high risk of relapse. Primary study objective was to assess feasibility and acceptance of this intervention by qualitative interviews with both participants and therapists, focusing on the following components: implementation of the concept of the continuation therapy, acceptance of medium telephone including length and frequency of phone calls, unfamiliarity of participant and therapist, and reciprocal influence of these components. Moreover, we assessed depressive symptoms, perceived self-efficacy for depression self-management, and working

alliance as quantitative measures to describe individual treatment courses. According to aims of pilot studies [174, 175] we used a mixed methods exploratory approach combining qualitative and quantitative measures to obtain in-depth understanding of this intervention including the new components, to later generate hypotheses for which individuals and under which circumstances this intervention might be adequate.

Intervention

This intervention is a low-intensity CBT-based continuation treatment provided for individuals who responded or remitted to a previous acute CBT, focusing on maintaining, reviewing and consolidation of skills acquired during this acute therapy, i.e., targeting prevention of relapse and recurrence. Thus, therapists were advised to discuss current concerns by reviewing skills the patient gained during acute psychotherapy and transfer and adapt these skills to the current situation in each session. Therapist procedures were supported by a manual which is based on guidelines in relapse prevention and continuation therapy in depression [39, 176, 177] and on a manual for telephone therapy in acute depressive disorder [178]. It contains a collection of strategies how to implement continuation treatment, keeping the participant motivated, strengthening his/her self-confidence and self-monitoring mood and behavior, formulated with specific reference to the medium telephone and persistent depressive disorder.

Within our study, participants received eight psychotherapeutic sessions over six months, approximately one session every four weeks. The first session was conducted face-to-face allowing room to form a sound relationship with the unfamiliar telephone therapist, to introduce the procedures of the next months, and to prepare a treatment plan. We chose employment of unfamiliar therapists accounting for flexibility which might be required for patients who received inpatient acute therapy by a therapist impossible to continue outpatient treatment. The subsequent seven sessions were conducted by telephone, varying only in

length of phone calls according to treatment condition (*30minC-TT* or *50minC-TT*). Acute phase treatment sessions commonly last 50 minutes in German-speaking areas. We wondered if 30 minutes of continued telephone therapy (*C-TT*) might be sufficient during a continuation phase treatment due to the specific focus of intervention (i.e. transfer of already acquired skills). Phone calls were initiated by the therapist located in a therapeutic unit, and patients were advised to choose an adequate undisturbed place. Irrespective of treatment condition, every phone session followed a structured procedure. After a short monitoring of depressive symptoms (PHQ-9) and current medication, therapist and participant reviewed home-work (optional) and discussed the main topic of the ongoing session. After assigning new homework (optional), therapist and participant scheduled the next session.

Psychotherapists were required to have a formal training in face-to-face CBT, permitted to treat patients in Switzerland. Monthly supervision for therapists was provided by the study team, to discuss treatment options and current health status of the included participants. Therapists followed a specific protocol to ensure safety in case of severe events, for example suicidality of a participant.

Participants

Subjects were considered eligible for participation if they aged 18 years or older, met criteria for persistent depressive disorder or recurrent depression according to DSM-5 [13], were currently in partial or full remission indicated by score of 9 or less on the Patient Health Questionnaire (PHQ-9), had completed a cognitive-behavioral oriented psychotherapy within the last six months before study enrolment, could speak and read Swiss-German or Standard German, and gave written informed consent. If subjects took antidepressant medication, long-term and stable dosage (i.e., unchanged drug intake for three months at least) was demanded for study enrolment. If subjects showed deviations regarding level of depressive symptoms or time of termination of previous treatment, decision for enrolment to the study was made on a

case by case discussion with the whole study team. Subjects were excluded if they met diagnostic criteria for acute suicidality, psychotic symptoms, severe cognitive impairments, or intended to stop antidepressant medication within the time of study participation. If necessary information couldn't be collected entirely within the screening interview, a research assistant contacted the subject's prior therapist to complete information with the subject's approval. If the participant's symptoms worsened during the treatment period, the therapist initiated adequate crisis management including transfer to acute treatment if necessary.

Setting and procedures

Several in- and outpatient centers in northern Switzerland were recruited during winter 2015, and requested to transfer patients to our psychotherapeutic unit who responded or remitted during acute therapy and were interested in continuation therapy. If individuals were considered eligible during a face-to-face screening interview, they were randomized to receive either *30minC-TT* or *50minC-TT*. Participants were kept uninformed that treatment conditions differed only in length of phone calls to avoid expectations that shorter contacts would be less effective. Following randomization a research assistant contacted the telephone therapist, providing all necessary information about the participant the therapist had to treat within the next six months. Face-to-face sessions were video-taped and therapeutic phone calls were audio-recorded.

Instruments

According to our primary study objective we assessed feasibility and acceptance with a semi-structured interview, using a guideline developed on previous work [179, 180]. Participants were interviewed after terminating treatment, and therapists were interviewed at the final phase of treating the last participant in the project. The guideline requested an open start into the interview, motivating the participant or therapist to describe general impressions of the intervention and study procedures, followed by discussing remaining questions of the

guideline. The interview focused specifically on evaluation of new components of intervention: acceptance of medium telephone including length and frequency of phone calls in context of continuation treatment in individuals being at high risk for relapse, and with unfamiliarity of participant and therapist.

According to reporting on individual treatment courses we assessed depression severity, depression-related self-management behavior and therapeutic alliance throughout therapy and at follow-up. *Patient's depression severity* was measured with the German self-report form of the nine item depression module of the Patient Health Questionnaire (PHQ-9) [181]. Participants are asked to complete the items in regard to the last two weeks ("How often have you been bothered by any of the following problems?"), rating the items on a four-point Likert scale ranging from 0 (not at all) to 3 (nearly every day). *Perceived self-efficacy for depression self-management* (PSDM) was assessed on six items in which participants indicate their belief and ability to cope with depression (e.g., confidence regarding overcoming depression, recognizing early warning signs, looking for professional help in time) on a ten-point Likert scale ranging from 0 (not at all confident) to 10 (extremely confident) [182]. *Therapeutic alliance* was measured by the 12-item Working Alliance inventory – short revised (WAI-SR) [183]. The client's form is rated on a five-point Likert scale ranging from 1 (rarely) to 5 (always), and assesses primary components of working alliance within three subscales: agreement of therapist and client on goals of treatment and how to reach treatment goals, and degree of confidence, trust and acceptance between client and therapist. All three instruments are considered reliable and valid measures in depressive disorders [182, 184, 185].

Data analysis

Semi-structured interviews of participants and therapists were audio-recorded and transcribed in standard German (Swiss German dialect was transformed into standard

German). Transcripts were entered electronically, and analyzed with the qualitative content analyses by Mayring [186] using the software MAXQDA (version 12) which is recommended in qualitative, quantitative & mixed methods research. As we had specific study objectives to evaluate feasibility and acceptance of the intervention we first applied a deductive approach, i.e., categories were predefined and raw material (interview statements) were allocated to these categories [187]. In a second step, statements within one category were ordered into sub-categories inductively to generate more specific themes. For verification of allocation to categories and themes, 10% of the statements were independently double coded within three subsequent trials to improve accuracy. Ambiguous cases were discussed and allocation redefined, accordingly. To ensure anonymity, participants' data are referred to as 'P1-7', and therapists' statements are referred to as 'T1/T2'. Quotes were translated into English by a non-native speaker. Quantitative data is reported in a descriptive manner displaying means and standard deviations, frequencies and percentages over time, comparatively in terms of treatment condition (*30minC-TT* or *50minC-TT*) before and after treatment and at follow-up (six months posttreatment). Additionally, depression severity is presented graphically as the PHQ-9 was assessed during each therapeutic session. Applying an *exploratory mixed-methods approach*, we combined qualitative and quantitative measures during analyses to better understand interaction between perceptions of new intervention components and a patient's individual course of symptoms (improvement, constancy, deterioration).

4.2.4 Results

Participants

Ten German-speaking participants contacted the study team or were referred by their prior (acute treatment) psychotherapists, respectively. Following the screening interview for eligibility, two participants decided to reject participation in the study for reasons as

preferring to join another study or not consenting videotapes and audio-recordings. We had to exclude one participant because previous psychotherapy had a vague orientation, and the previous therapist was not accessible by email or phone and no clinical report was available. Three of the remaining seven participants were randomized to receive *30min-C-TT* while the other four participants received *50minC-TT*. All seven participants completed the intervention with two exceptions: Mental health status of one participant receiving *30minC-TT* worsened after the fourth phone call, requiring a referral to an acute treatment. During referral phase this participant received the remaining three phone calls until referral was completed. One other participant receiving *50minC-TT* terminated treatment already after the fifth phone call because he declared not to need any more treatment due to feeling stable.

Baseline socio-demographic and clinical characteristics of randomized participants are displayed in table 3, comparatively in terms of treatment condition. With respect to the small sample size balance between treatment conditions was not present. Most of the participants were single or divorced-separated, and varied regarding their employment status. Whilst three participants were referred to by their acute treatment therapist from inpatient psychiatry, the other four participants got informed about the study by public media and had prior outpatient acute treatment. Number of previous psychological treatments was nearly balanced between both conditions, and the majority of the participants took parallel antidepressant medication. All participants had either recurrent depression with incomplete remission between episodes or double depression (superimposition of a major depressive episode on antecedent dysthymia) before entering previous acute treatment, and an initial depression severity level indicating no symptoms (*50minC-TT*) or minimal symptoms (*30minC-TT*) on average [181]. All therapies were delivered by two female professional psychotherapists having eight years of clinical experience, and both therapists treated participants in both treatment conditions.

Table 3 *Baseline characteristics of participants at baseline*

	30minC-TT[a] (*N* = 3)	50minC-TT[b] (*N* = 4)
Gender (female), *n*	2	1
Age, *M (SD)*[c]	43.7 (11.9)	54.8 (9.6)
Marital status, *n*		
Single	0	2
Married	1	0
Divorced–separated	2	2
Employment, *n*		
Full time	0	1
Part time	1	1
Unemployed	2	0
Retired	0	1
Supported	0	1
Referral, *n*		
Psychologist/psychiatrist	1	2
Media	2	2
Number of previous psychological treatments, *M (SD)*[c]		
Inpatient	2.3 (2.5)	2.5 (1.7)
Outpatient	1.7 (0.6)	2.5 (1.7)
Last previous (acute) treatment, *n*		
Inpatient	1	2
Outpatient	2	2
Current antidepressant medication, *n*	2	4
Diagnostic subgroup, *n*		
Pure dysthymia	0	0
Chronic major depressive episode	0	0
Double depression	2	2
Recurrent depression, incomplete remission between episodes	1	2
Recurrent depression, complete remission between episodes	0	0
Depression severity (PHQ-9)[d]	8.3 (7.2)	4 (2.2)

[a] *Continued telephone therapy, 30 minutes phone calls*
[b] *Continued telephone therapy, 50 minutes phone calls*
[c] *Mean (M) and standard deviation (SD)*
[d] *PHQ-9… Patient Health Questionnaire*

Individual treatment courses

Participants differed considerably in course of outcome measures during and following treatment, but already before entering continuation treatment (see table 4). With respect to individual development of depressive symptoms two participants improved (P3, P5), three remained more or less on their initial severity level (P2, P6, P7), and two others deteriorated (P1, P4) during treatment (see figure 16). Whilst most participants showed a slight to moderate increase of symptoms at six months follow-up, one participant (P4) showed less symptoms compared to posttreatment. During the subsequent report of qualitative analyses we will refer to data displayed in table 4 and figure 16, discussing potential associations between interview statements and quantitative data.

Table 4 *Quantitative measures of course of treatment compared across treatment conditions*

	Pre-treatment		Post-treatment		Follow-up (6 months)	
	30minC-TT[a]	50minC-TT[b]	30minC-TT[a]	50minC-TT[b]	30minC-TT[a]	50minC-TT[b]
	n = 3	*n* = 4	*n* = 3	*n* = 4	*n* = 2	*n* = 3
PHQ-9[c]	9.7 (8.5)	5.5 (2.5)	10.3 (2.1)	4.7 (5.7)	11.5 (2.1)	6.7 (1.5)
PSDM[d]	36.0 (19.3)	41.3 (8.5)	22.0 (15.9)	46.0 (9.4)	28.5 (6.4)	39.0 (2.0)
WAI-C[e]	3.9 (1.2)	4.3 (0.4)	3.9 (0.8)	4.6 (0.4)	-	-

[a] *Continued telephone therapy, 30 minutes phone calls*
[b] *Continued telephone therapy, 50 minutes phone calls*
[c] *Patient health questionnaire (sum scores ranging between 0 and 27)*
[d] *Perceived self-efficacy for depression self-management (sum scores ranging from 0 to 60)*
[e] *Working Alliance Inventory, client's form, mean scores ranging from 1 to 5*
[c-e] *Standard deviations are indicated by brackets (SD)*

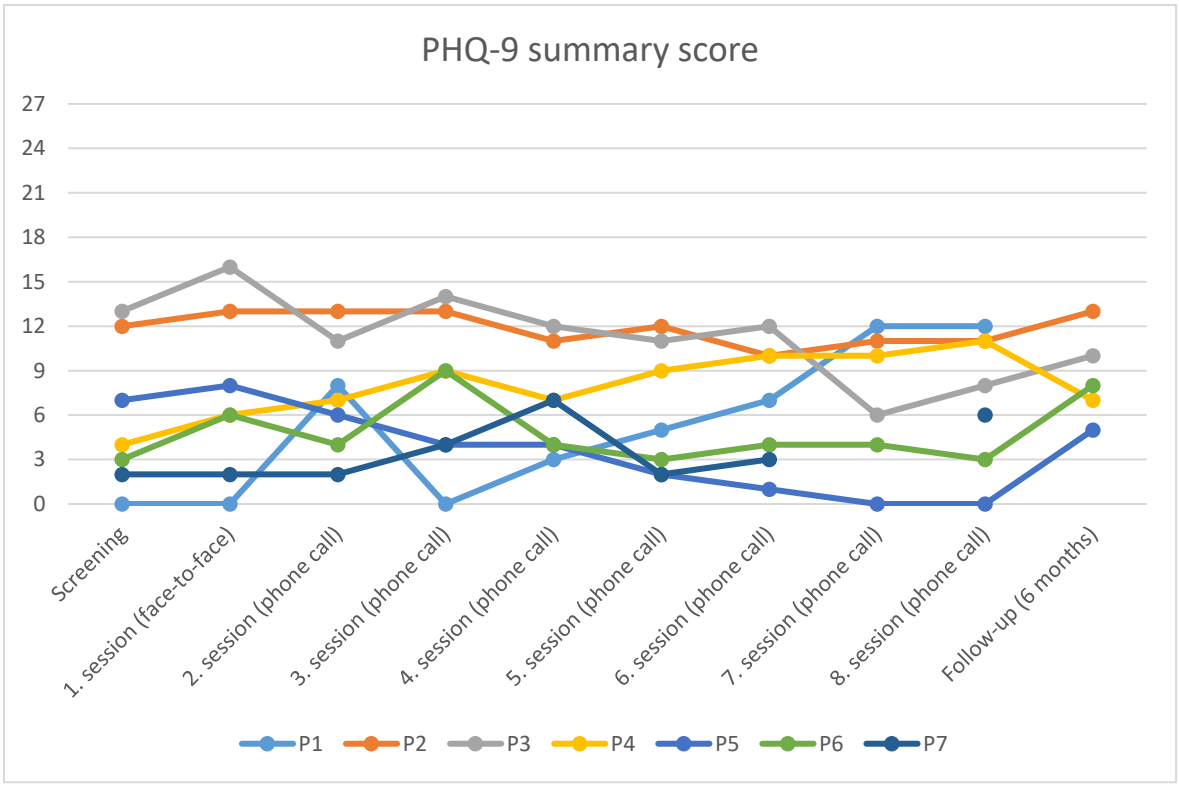

Figure 16. Course of depressive symptoms.
Measured with the Patient Health Questionnaire (PHQ-9) during each session and at follow-up (six months posttreatment), displayed for the seven participants. Participants P1-P3 received *30minC-TT*, participants P4-7 received *50minC-TT*.

Feasibility and acceptance of intervention components

Five of seven participants agreed on conducting an interview after terminating treatment. One participant had to undergo surgery after terminating treatment, and was thus not able to join an interview. The other participant did not join an interview without stating reasons. Both therapists agreed on participating the interview. During analyses two main topics emerged: (1) Acceptance of medium telephone, and (2) Feasibility of the provided continuation therapy regarding aim of intervention, previous treatment, and length and frequency of sessions.

(1) Acceptance of medium telephone

Within this topic, two main themes emerged from the analysis.

Alliance and communication

Most participants and therapists were positively surprised that they could speak openly about anything on the phone with an unfamiliar person, perceiving telephone setting different but not worse compared to face-to-face settings:

> *"The first phone calls required getting used to it. I never had this over the phone. During the first sessions, I did not contribute so much, because, especially during the first calls you do not know each other so well, you are approaching the other one. It takes quite a while until you open yourself, you are not starting right away. Approximately after the first two, three calls it went really well. We appreciated each other very well and had no holding backs. Yes, summarized, very positive." (P3, 30minC-TT)*

However, development of a sound therapeutic relationship with an unfamiliar therapist was considered feasible only with an initial face-to-face session beforehand:

> *"You should invest one or two hours. I mean, also for a therapist it is important to know where the patient got stuck, where does the patient needs support. I think that is important. And also to see the person. You need to establish a personal relationship, a bond of trust. I do not think, that this is possible entirely over the phone." (P7, 50minC-TT)*

All therapists and participants noted that nonverbal signs were missing. For most participants it seemed to have no substantial influence on quality of trust or understanding, also reflected by high scores on the working alliance inventory (see table 4, p. 128), which are comparable to scores reported in face-to-face outpatient settings [185]. However, one participant perceived medium telephone as insufficient setting for fitting her needs, and this very participant showed moderate depressive symptoms throughout therapy and reported to not have benefitted from this intervention at all.

> *"It was easy to keep a good therapeutic relationship over the entire therapy [over the phone], always allowing to intensify the relationship." (T2)*

> *"In a face-to-face conversation, I see gestures and mimics of my therapist, her reactions, and I missed that on the phone … [I had the feeling] that she [the therapist] could less emphasize into my feelings. Maybe because she did not see me, just listened to what I told her … although telephone is actually a personal form of contact, I prefer [therapeutic] conversations with visual contact with the therapist" (P2, 30minC-TT)*

Also, having no facial contact was associated with a potential risk of being less present towards the patient. Another therapist tried to compensate missing cues by adapting language.

> *„Still, I see the potential to make myself a bit more comfortable, isn't it? As a therapist, I mean, the patient cannot see me. And it might happen that I am a bit less present. And I consider this a bigger risk compared to face-to-face." (T1)*

> *"I speak much slower and more precise compared to face-to-face. This is a rather mechanical aspect. But I have the impression, this generates attention if I speak slowly and understandable." (T2)*

Location and time

Participants associated telephone with an advantage of logistic flexibility in terms of choosing a suitable place, spending no time for journey or being independent from external factors, especially when living in rural areas. However, agreeing on day and time of the next session was perceived comparable to face-to-face settings, and therapists noted that employed participants preferred appointments pre- or after working hours.

> *"Especially for me, I do not have a car, no driver's license, and then, for me it always needs a bit more effort going anywhere. And now, I was just home, knowing that the phone would ring … interestingly, I talk differently when being home. I feel more save, familiar surroundings. I am the type of person who walks around the flat while phoning." (P7, 50minC-TT)*

However, flexibility was not always considered an advantage compared to face-to-face settings. Although participants were advised to choose an undisturbed place, and most participants chose home or an empty office room for calling, daily circumstances (e.g., job or family commitments) might hamper readiness for therapy. Consequently, therapists should

discuss the importance of a quiet and undisturbed therapeutic setting together with the patient before starting telephone therapy, and if and how such a setting can be ensured.

> *"Once I called while sitting in the train because it did not work elsewhere. And sometimes I called from home, but I could not speak so well there either. For me, it would be better during evenings when my children are not around … yes, like here, a quiet neutral room like in a private praxis, where you are not distracted from other things … that's better" (P2, 30minC-TT)*

(2) Feasibility of continuation therapy

Within this topic, three main themes emerged from the analysis.

Aim and focus of continuation therapy

Most participants received aim and focus of continuation therapy as valuable and different from therapies they received before. They valued continued care in terms of longer and frequent support after terminating therapy and maintaining the gains of acute therapy by focusing on the future, especially regarding the persistent and recurrent character of depression.

> *"Most notably, this [concept] was future-oriented, finding approaches to prevent relapse and to live with my illness instead of forcing to solve the past … and this concept of continued care was new for me … usually, you have to get along with it alone. But due to helping me maintaining strategies, I did not feel as lonely as following other therapies" (P5, 50minC-TT)*
> *"Also, to give myself time: can I manage that on my own? And if not, I have a lifeline which I can call or write to, who is there for me ... If I should stumble, this is ok because I have someone who helps me to get back on my feet. And then, I have to get along on my own again. I cannot rest on this. This illness is deceitful. I cannot rest until it became ingrained, as automatisms. I have to monitor myself every day. There is no other way." (P7, 50minC-TT)*

These two participants started with low level of symptoms, maintained on that level or even improved during treatment, and received 50 minutes phone calls (see figure 16, p. 129). By contrast, one participant expressed her disappointment with the intervention. She perceived no fit between her needs and concept of low-intensity treatment, wishing to have

received more frequent therapy in retrospect, indicating that concept of continuation therapy was probably not quite clear:

> *"I think during this time [continuation therapy] other topics were relevant. And I think, not so much connection was made to previous [therapy]… I had expected to get support further on, for preventing. And if the therapist notices that there is more demand for action, to begin there …. Going more to the basis, what are triggers I am feeling exactly this way? Just, more digging into it." (P2, 30minC-TT)*

This very participant entered continuation therapy with moderate levels of depressive symptoms, received 30 minutes phone calls, and additionally reported on difficult personal circumstances (unclear employment status, relationship issues). For this participant it might had been better to undergo further acute treatment because the combination of these conditions hampered implementation of effective continuation therapy, which we assume was amplified by medium telephone and an unfamiliar therapist. Another participant (P3) showed a similar course of depressive symptoms until the sixth' session, received 30 minutes phone calls (see figure 16, p. 129), and also reported on difficult personal circumstances. However, this participant seemed to have adjusted to aim and context of the intervention and reported to have benefitted from the intervention, also shown by decreasing symptoms during the last two sessions:

> *"I expected usual psychotherapeutic appointments, just shorter and over telephone ... and the first phone calls, I perceived them as too short, and I wondered: will this work? … we spoke a lot about what I had learned during previous therapy to manage similar situations. And I also learned some new good bets. It was a mix between previous and new insights, well done!" (P3, 30minC-TT)*

To constantly focus on consolidating strategies requires an explicit therapy plan pursued throughout limited sessions of continuation therapy, and therapists perceived this as a main challenge in terms of organization each session:

> *"Yes, the challenge is the switch between acute and continuation phase. The challenge is, that you really do formulate therapy aims and a treatment plan right in the beginning. And having the focus on maintenance and stabilization that the patient can handle this on his/her own in the long-term. And that you organize each phone call in this regard. Because, there are some patients who speak about what happened, and so forth … you should prevent the patient of talking 15 minutes about any problem and then developing something on that … yes, it has to be clear, this is the treatment plan, stick to that." (T1)*

Both participants and therapists would appreciate a formal integration of continuation therapy into the health care system to ensure that patients at high risk are actually monitored following acute therapy. Moreover, this might lower the threshold of contacting a therapist again, and by this, contributing to long-term stabilization:

> *"I hope that this will find a way into daily treatment of patients that this idea of continued care will be a topic in therapists … because this was not a topic in my previous therapies. Of course, they told me that that I can call them if I should worsen. But then, I feel like a loser, if I call them." (P5, 50minC-TT)*

> *"Because, of course, if acute therapy is terminated, the patient is usually not monitored anymore. Or the patient is not making contact again with a therapist if he/she gets worse. And for this, this concept is ideal … would be nice to have this offer that a patient can contact the therapist in such a formal frame. I think such a quick access to therapy could prevent … it might contribute that individuals get better, are stable in long-term." (T2)*

Dependency on gains of precedent acute therapy

As continuation therapy should be provided only to patients who at least responded to acute treatment, we allowed our participants to show minimal depressive symptoms as indicated by a PHQ-9 score less than 10 by study entry. However, two participants (P2, P3) showed higher scores (see figure 16, p. 129), but previous therapists affirmed stability of patients and eligibility for a continuation program. Although initial level of depressive symptoms seemed to influence course of continuation therapy in some way, therapists considered gains of acute therapy in terms of skills and tools a patient has as another important aspect for successful implementation of a continuation therapy. This might be especially an issue when patient and therapist are unfamiliar because patients can explain their

set of strategies during the first session to the therapist, but proving whether they actually work and are considered helpful happens later during therapy, and therapists have to work with what the patient brings with him/her:

> *"Practically, in my patients there was simply not that huge tool box you could use well-structured during all sessions. This was the crux. Often, we spoke about current concerns. And not in the light of how the patient learned to solve this, but rather that there was even no well-known strategy available. For instance, in this one patient [P2], she had so many "building sites", that we focused on finding or developing strategies because she had no "portfolio of resources" she considered helpful… thus, it was rather a mix of acute and continuation therapy… I tried always to address "Remember, what was helpful last time? What did you do?" (T2)*

Moderate level of depressive symptoms of the mentioned participant (P2) remained rather stable during treatment (see figure 16, p. 129). At the same time, the participant reported on low level of self-efficacy for depression management at posttreatment (PSDM; see table 4, p. 128), which might have contributed to her perception to not have benefitted from the intervention at all. By contrast, in other participants continuation therapy worked very well, possibly supported by a short interval between acute and continuation therapy, which also enhances remembering strategies. Especially patients receiving *50minC-TT* reported to have benefitted from the intervention, and showed higher levels of perceived self-efficacy for depression self-management throughout therapy (see table 4, p. 128).

> *"He (P7) really has a huge tool box. He not only has one, he is benefitting a lot, using it every day. We could focus on that during sessions. He completes these situational analyses. He always moves himself on the observer perspective, what does he need, and he claims his needs. This was really ever-present, all skills from acute therapy… In this patient, acute therapy was not that long ago as in the other patients." (T1)*

> *"Maybe it would be good to have continuation therapy quite after acute therapy, if this is possible… This would be interesting because memory lowers… yes, that you remember what you actually spoke about [during acute therapy] … yes, you remember conversations roughly, but relatively little." (P4, 50minC-TT)*

The previous mentioned issues (patient's skills, personal circumstances, functionality, needs, history of illness) might be best addressed by a continuous provider, as reported by both participants and therapists. However, working together with an unfamiliar therapist is assumed feasible due to aim and focus of continued care, which is considered in consolidating gains of previous therapy.

> *"This was the good thing. I did not have to start again with Adam and Eva. Instead, it had a focus on the future … [in previous therapies] I had the feeling the first sessions had been only for the therapist, and after that, it was about me. And now, this could be omitted." (P5, 50min)*

Frequency and length of sessions

Whilst mean length of phone calls was around 33 minutes in *30minC-TT*, mean length of phone calls was around 43 minutes in *50minC-TT*. This is in line with impressions from the interviews as both therapists and participants received 30 minutes each month as definitely too short to benefit while 50 minutes was not always perceived a necessary length for each session. However, organizing own concerns within limited time was considered a challenge, and moreover an ability you have to acquire during continuation therapy:

> *"You are just starting, you are getting into it, you know it is going on, and then "Hmm, we have to stop" …. And I looked strategically, what will have place within the next ten minutes, and what will have not? And then I just left out something. I had to learn to organize myself…. Because in the beginning we talk about my last month, how I felt. And if we would then also talk about what we discussed during the last session, there would be no time for things that concern me currently." (P3, 30minC-TT)*

> *"30 minutes. For some people this might be too less. The question is, can I point out what is important for me? I mean, I could tell all my things from the last month, and then this will take three hours, approximately. This is the risk. You must have to point out, what is your topic today, what is important I want to speak about." (P7, 50minC-TT)*

Phone sessions were conducted approximately each four weeks. There was a trend that participants receiving *30minC-TT* (who showed higher levels of depressive symptoms already by study entry, see table 4, p. 128) perceived a one-month gap as too short compared to participants receiving *50minC-TT* (who showed less depressive symptoms throughout the

study). Moreover, participants mentioned that this gap requires prioritizing of your concerns, and that longer intervals between sessions is exactly the adequate setting needed for making the progress stepping from acute to continuation therapy:

> *"Think, ok, we have just a few sessions, where do I want to emphasize? I have so many things we could speak about …. and yes, in the beginning of therapy I wished to have therapy more often. But then, later, I realized, it is continuation therapy. And this means, I have to get along with some things on my own now. I have to bite through until the next session" (P3, 30minC-TT)*

> *"If you would go to the therapist every week, maybe there is no need for that, [because] then you would have again a dependency of relationship in which you can lean back and say 'I will discuss this next week'… and really try to get along alone during this interval, without calling each time 'please help me' or 'what shall I do?', this is actually the crucial point, to learn to walk on your own." (P7, 50minC-TT)*

Although participants perceived a one-month between phone calls as generally adequate they recommended entering continuation treatment with shorter intervals followed by extending these intervals, to have a "softer" transition from acute phase to continuation phase setting:

> *"Yes, if one had finished [acute] therapy just recently, I imagine this might be too less. Maybe, once in two weeks, and later then, once a month, bit by bit. That intervals become longer. This would be desirable." (P3, 30minC-TT)*

This one-month interval between sessions was associated with perceived challenges in linking contents of these sessions, probably solved by making detailed notes about the past and prospective contents of sessions. Moreover, therapists discussed opportunities and challenges of in-between contacts as short emails regarding homework or smaller concerns.

> *"Yes, you lose linkage, remembering the last session is hard. You make notes, but it is still hard to remember the last conversation, to put yourself back there… you should write a protocol for yourself, regularly. This would be an option." (P4, 50minC-TT)*

> *"Nevertheless, I had the feeling some patients benefitted from writing me and I wrote back… an advantage is that it helps to keep alliance and to stay in the [therapeutic] process. A disadvantage is that this takes time, and that contacts are intensified… although you want to keep it at low-intensity level." (T2)*

4.2.5 Discussion

Aim of the study was to evaluate the feasibility and acceptance of a telephone-based continuation therapy for individuals at high risk for relapse into depression. We used an exploratory mixed-methods approach to obtain detailed understanding of this intervention including evaluation of the new components, i.e., medium telephone including length and frequency of phone calls in context of a continuation treatment with unfamiliarity of participant and therapist.

We consider an effective implementation of the proposed intervention as feasible if several preconditions are ensured. *First*, the previous acute treatment has to be terminated successfully defined by a low or minimal level of depressive symptoms. Moreover, the patient had to acquire strategies to effectively cope with concerns or difficult circumstances independently. If both factors are ensured we consider likelihood of an effective continuation treatment including maintaining or improving mental health status as high. By contrast, for patients still showing moderate level of depressive symptoms by only a little range of effective coping strategies we consider the application of a low-intensity intervention as we provided as inadequate. Studies show that even after terminating depression treatment 30% to 50% of individuals report on residual symptoms [188–191], and these are associated with enhanced likelihood for prompter relapse up to three times [188]. This might be even increased in recurrent and persistent depressed individuals due to a potentially underlying

vulnerability, which is considered premorbid or has developed with accumulated depressive episodes [1]. Thus, even though patients might benefit from a low-intensity continuation intervention indicated by stable symptomatology/residual symptoms, superficial aim should be to further decrease level of depressive symptoms, which might be better addressed by a higher frequent acute therapy.

Besides level of depressive symptoms, our therapists also highlighted the importance of available coping strategies. An acute-phase depression CBT study [113] investigated coping self-efficacy (using problem-focused coping, stopping unpleasant emotions and thoughts, getting support from others) [192], and found that moderate to high levels of coping self-efficacy significantly increased likelihood of responding to CBT, irrespective of treatment delivery (face-to-face vs telephone) [193]. In our study we assessed perceived self-efficacy with depression management (PSDM), which shares aspects with coping self-efficacy. We also observed in our participants with lower levels of depressive symptoms higher scores on the PSDM by entering continuation therapy, and even increasing PSDM scores by end of intervention, underlining the importance of coping strategies throughout treatment and across treatment phases.

Second, a continuous provider enhances likelihood of valid assessment of patient's response/remission status and coping strategies by terminating acute therapy. However, change of therapist between acute and continuation treatment phase is feasible if preconditions as outlined above are ensured and records on previous treatments are transferred to the new therapist. Change of providers is a common condition in health care systems in which funding of outpatient and inpatient treatment is covered by separate parties. Consequently, consistency of care between acute inpatient to continuation outpatient treatment might be impaired, and mistreatment or variation in prescribed medication can occur [194]. Several approaches as integration of general practitioners into both in- and outpatient treatments, electronical storing of medical patient data, and implementation of

standardized cover letters are discussed for improving communication between providers [194].

Third, application of medium telephone was mostly addressed by well-known advantages as low-threshold access with personal contact, omission of drive to therapy (which is especially relevant for individuals living in rural areas or for those being physically impaired), and a more flexible integration of therapy into everyday life including job and family responsibilities [113, 117]. Those factors might enhance likelihood that high risk patients maintain in therapy even after successful acute treatment to sustain remission and recovery in the long-term. Also, telephone is recommended for treatments having a lower level of complexity by showing a medium level of comprehensiveness [110], and thus might especially qualify for mode of delivery of continuation treatments: Acute treatments intend to reduce patient's symptoms and work towards understanding of development and maintenance of the patient's depression. Whilst these processes are considered rather complex, continuation treatments aim to practice and intensify relapse prevention techniques already acquired during acute treatment, and telephone might be an adequate medium for this level of complexity. Our therapists mentioned two further issues to ensure when applying telephone: a stronger consideration of precise language, intonation and verbal cues [113], as well as a clear agreement with the patient on location for phone calls to avoid disturbed settings [178].

Fourth, evaluation of length and frequency of sessions during the continuation treatment phase varied in regard to level of depressive symptoms and attitude towards the intervention concept. If participants showed moderate depressive symptoms and expected to receive high-intensity treatment, 30 minutes was perceived as inadequate and not fitting the participant's needs. The 'adequacy of fit' between type of intervention, medium of delivery and patient's concept of what a therapy represents is considered relevant to embark in therapy and benefit from it [117]. Both participants and therapists would have preferred the 50 minutes condition considering the one-month gap in-between sessions, to ensure integration

of symptom monitoring, reviewing home-work, discussing current concerns with regard to available strategies, and scheduling exercises and the next session. Other psychotherapeutic continuation interventions for recurrent or persistent depressed individuals apply a 50 or 60 minutes setting [67, 137], even allowing an extension up to 90 minutes [136]. Moreover, those interventions usually start with biweekly sessions, passing over to one session per month.

One of our therapists and one participant also recommended to determine only the number of sessions within a fixed time period, but allowing to choose frequency of sessions independently, including more frequent sessions directly after transition from acute to continuation treatment phase. However, three of our participants explicitly supported the application of a one-month interval between sessions to actually have time for practicing the consolidation of skills acquired during acute therapy. But this one-month gap was also associated with difficulties in making the link between the last and subsequent session. A stronger structure within a session and a clear treatment plan across the entire treatment period might help to prioritize contents of each session, and making a link between sessions. Also mandatory homework for reworking issues of the past session and reviewing the results of this homework at the next session could help to make a clear link between sessions over time, and in parallel, can contribute to increase of patient's functioning [195].

Fifth, we determined a six-month treatment period based on clinical guidelines who recommend a period between four and nine months [6, 45], and with regard to other psychotherapeutic continuation interventions who last between four and eight months [67, 137]. The majority of our participants wished to have received longer continuation treatment, especially those who deteriorated during treatment or still showed moderate depressive symptoms by end of intervention. Four of five participants who provided follow-up data showed a slight to moderate increase in depressive symptoms after six month posttreatment. Considering the recurrent and persistent condition of our participants a subsequent

maintenance therapy might enhance relapse-preventive effects for individuals being at high risk even after successful acute and continuation treatment [6, 45].

Long-term psychological and pharmacological maintenance treatments up to three years promise relapse-preventive effects in recurrent and persistent depressed individuals [62, 65, 70, 169, 196, 197], and they usually provide the same treatment during all treatment phases. *Sixth*, there are interventions which provide remitted or recovered patients with continuation treatment irrespective of previous treatment(s). In recent years, the Mindfulness-Based Cognitive Therapy (MBCT) [48] obtained attention in research and clinical practice, and is considered a promising approach in reducing relapse and recurrence in individuals, which experienced more than three depressive episodes [47]. MBCT is an eight-week intervention conducted as group therapy with weekly meetings and imparting strategies specific to the underlying theory of this intervention. Thus, this program differs from continuation treatments as explained above due to its rather short-term format and lack of explicit linking to previous treatments. Whilst our intervention is reliant on patient's available strategies and rather immediate transition between acute and continuation treatment, MBCT has less restrictions and might provide a further or additional approach to sustain relapse and remission in the long-term.

Finally, despite high demands, long-term psychotherapeutic continuation or maintenance interventions are currently not an integral part of standard mental health care [3]. This might be owed to progressively limited financial resources of the health care system, resulting in a lack of systematic and comprehensive networks of providers and treatment options. In outpatient settings therapists might offer 'booster sessions', which share components with continuation programs, as reviewing or reactivating the learned from therapy [198]. However, such booster sessions are commonly taking place only on the patient's request and are not scheduled in advance. One of our participants mentioned that after terminating acute therapy she felt stable and was in no need for further treatment, and

did not make use of booster sessions consequently. Later, by the time she deteriorated, she felt ashamed of contacting her therapist again. This highlights the value and need of a formal integration of continuation interventions into the health care system to ensure continuous long-term monitoring of patients being at high risk for relapse and recurrence.

Strength and limitations of this study need to be considered when interpreting the found results. To our knowledge, this is the first study providing continued psychotherapeutic treatment to people with recurrent or persistent depressive disorder over telephone. Before effectiveness of an intervention can be evaluated it is recommended to assess quantitative as well as qualitative data within a feasibility trial to obtain detailed understanding of the intervention including aspects which already work well, but also problems in implementation [174, 175]. Hence, we conducted a pilot study to assess feasibility of this intervention evaluated by both participants and therapists using qualitative and quantitative methods, which we consider a key strength of this study as it investigated each new intervention component and interaction of these components. However, due its pilot character the study has some limitations. Findings are based on seven participants and two therapists who were motivated and engaged into this research project, raising question on the generalizability to routine care settings. The study was conducted in Switzerland and addressed characteristics specifically to the Swiss health care system, which might differ regarding format and funding of treatment from other countries. Moreover, we were not able to analyze quantitative measures on course of treatment statistically, and neither included an untreated control group. Hence, we do not know if and how our intervention accounts for changes we observed in participants. Also, not all participants completed all measures and two participants did not join the interview, probably biasing the results considering the small sample size.

Findings of this pilot study have important implications for further development of continued psychotherapy for depressed individuals at high risk for relapse and recurrence. Most studies to date investigate pharmacological long-term treatments assuming relapse

preventive effects in high risk individuals. At the same time, patients report on severe side-effects resulting in discontinuing antidepressant medication without the doctor's agreement, which in turn increases likelihood of relapse. Psychological long-term interventions can meet this condition by focusing on enduring behavioral change which might be less associated with adverse events. Moreover, as individuals with recurrent or persistent depression commonly take antidepressant medication, psychotherapy might support relevance and continuous intake of drugs. Barriers on several levels (patient, provider, health care system) do hamper access to treatment, and telephone is considered a promising approach to provide more patients with low-threshold care by showing characteristics similar to face-to-face settings. However, this pilot study cannot draw any conclusions on the effectiveness of this intervention due to discussed limitations. But, findings of this project influenced further development of the intervention, and is going to be investigated for its effectiveness within an ongoing multi-center randomized controlled trial organized by our department, comparing the telephone-based continuation therapy against treatment as usual (NCT03219879).

Conclusion

The present findings provide in-depth insight to opportunities and boundaries of a telephone-based psychotherapeutic continuation program for people with recurrent or persistent depressive disorder. While participants and therapists evaluated the concept and aim of this intervention as feasible, and considered telephone as an adequate medium for this treatment phase, there are factors which need to be taken into account for deciding which individuals might benefit from this intervention. Low level of residual symptoms and available effective coping strategies are core conditions which need to be ensured before terminating acute and entering continuation therapy. A clear treatment plan implemented throughout therapy and prioritizing of contents within each session is required by both patients and therapists due to limited sessions and longer intervals between sessions. If those

aspects are fulfilled, medium telephone is considered feasible and moreover, might facilitate access to long-term treatment for individuals at high risk of relapse or recurrence.

4.3 Identifying relapse prevention elements during psychological treatment of depression: Development of an observer-based rating[6] instrument

4.3.1 Abstract

Background. Although observer-rated instruments assessing therapist's adherence to relapse-preventive treatments are available, they do not adequately cover specific relapse-preventive elements that focus on implementation of strategies after terminating treatment. This study describes the development of the KERI-D (**K**odierbogen zur **E**rfassung **R**ückfallprophylaktischer **I**nterventionen bei **D**epression/Coding System to Assess Interventions of Relapse Prevention in Depression). The KERI-D is a new observer-based rating tool for acute or continuation/maintenance-phase sessions and assesses relapse-prevention elements including implementation into patient's daily routines.

Methods. The development of the KERI-D included iterative steps referring to theoretical, clinical and empirical sources. It consists of 19 content items within four categories (self-care, early warning signs, triggering events/situations, termination of therapy) and one global item. For empirical analyses, videotaped psychotherapy sessions of 36 psychotherapies were rated by three independent observers and analyzed for their psychometric properties.

Results. Most items showed moderate to good inter-rater reliability (median ICC = .80) and retest reliability (median ICC = .93). Principal-axis factor analysis revealed three subscales, and first evidence of content validity was demonstrated. No associations with clinical follow-up data were found.

Limitations. Analysis was limited to a relatively small sample of selected psychotherapy sessions. Evaluation of predictive validity is a desirable next step to further examine applicability and scope of the instrument.

[6] For a similar version of this chapter see [199].

Conclusions. The KERI-D is the first observer-based rating instrument measuring specific relapse-prevention strategies in psychotherapy for depression. It may help to identify elements that prove effective in reducing relapse/recurrence in the long-term and thereby help to optimize effect duration of depression treatment.

4.3.2 Background

Psychotherapy research on the effective prevention of relapse and recurrence after acute depression treatments has mostly investigated cognitive behavioral interventions, both alone and in combination with antidepressants [12, 137, 200]. However, after a terminated acute phase of cognitive behavioral therapy (CBT), relapse/recurrence rates were found to be 29% in the first year and 54% in the second year [12]. Even with continued/maintained psychotherapy or pharmacotherapy, relapse and recurrence rates are still found to be high [12]. Considering generally high relapse rates in depression, it is essential to identify potentially underlying processes of relapse prevention, followed by an investigation of their effectiveness and related mechanisms of action. Although treatment manuals recommend a variety of relapse-prevention elements, available measures assessing therapists' treatment adherence and competence only marginally target relapse-preventive aspects beyond core cognitive treatment elements (e.g., CT techniques).

Three types of psychological interventions target the prevention of recurrence of depressive symptoms [38]: 1. Interventions *during acute treatment* aiming to maintain reduced symptoms also beyond termination. 2. Continuation and/or 3. Maintenance treatment, both provided *after terminating acute treatment*. Whilst continuation treatments are provided to currently remitted patients or to patients that previously responded to treatment, maintenance treatments are given during recovery defined as remission lasting longer than six months [7, 8]. All three types of interventions intend to prevent patients from experiencing

relapse (return of depressive symptoms before full remission has been achieved) or recurrence (appearance of another new episode of depression after full remission) [8].

Established treatment manuals for cognitive and interpersonal therapies [176, 201–204] include specific recommendations for relapse prevention techniques being mostly assigned to the final phase of therapy. More specifically, elements to rehearse in this treatment phase include: early detection of depressive symptoms, anticipating critical situations and adequate coping skills, maintaining antidepressant activities, reinforcing helpful cognitions, planning the future, sensitizing the patient to potential relapses, and preparing transition from therapy to time after therapy termination. Although a variety of relapse prevention strategies seem to be recommended and commonly used in clinical practice, instruments measuring the quantity and quality of specific relapse-prevention elements have not yet been developed. More specifically, available scales assessing adherence and competence during psychotherapy do not fully cover the adequate implementation of relapse-prevention techniques beyond core treatment elements (e.g., central cognitions in CT).

In psychotherapy research, treatment integrity is defined by adherence and competence [77]. *Adherence* is defined as the degree a therapist provides interventions as determined in the treatment manual, whereas *competence* is defined as the extent to which a therapist implements such techniques in a skillful manner. A variety of reliable and validated instruments assessing therapist's adherence and competence during psychotherapy are available. The most influential adherence scale is the Collaborative Study Psychotherapy Rating Scale [CSPRS; 80], developed to assess treatment integrity in CBT, interpersonal therapy, and psychiatric clinical management, including also particular CBT techniques (e.g., recognizing cognitive errors) observed in-session [205]. Referring specifically to relapse prevention after terminated acute treatment in individual setting, only one scale is available: The Cognitive-Behavioral Maintenance Therapy—Adherence Scale (CBMT-AS) was developed in the context of cognitive-behavioral maintenance therapy to assess therapists'

adherence to the manual of relapse-prevention therapy for recurrent depressive disorder [206]. Besides global evaluations ("management of time") and cognitive-behavioral contents ("Encouragement of self-monitoring"), also one "relapse prevention" item is included. However, this single item was not used in further analyses because it was considered to be insufficiently assessable during therapy sessions [206].

The most influential competence scale is the validated and frequently applied Cognitive Therapy Scale [CTS; 81]. It is an observer-based rating instrument containing items on general competencies (e.g., use of feedback and summaries), specific competencies (e.g., focus on central cognitions), and one global item (overall rating of competence). Evidence for associations of competence and adherence measures with clinical outcomes in cognitive treatments for depression is equivocal. The meta-analysis of Webb and colleagues [79] found no significant associations, which the authors attributed to the variety of applied methods (rating instrument, number of rated sessions, etc.), or to little influence of therapists' adherence and competence on patients' symptom change.

The mentioned instruments target relapse-preventive elements only to a marginal degree, i.e., items such as 'Encouragement of self-monitoring' or 'relapse prevention' [e.g., CBMT-AS; 206], and these instruments focus rather on the application of certain behaviors during treatment than preparing for their application after discontinuing treatment. Thus, there is a need for an instrument assessing specific relapse-preventive elements initiated by the therapist which focus on the patient's implementation of strategies after termination of treatment, such as anticipating critical situations or sensitizing the patient to potential relapses and recurrences in the long-term.

Aim of the present study was to create a rating instrument to systematically assess relapse-preventive elements during CBT for depression. For this, we developed the KERI-D (**K**odierbogen zur **E**rfassung **R**ückfallprophylaktischer **I**nterventionen bei **D**epression/Coding System to Assess Interventions of Relapse Prevention in Depression), an observer-based

rating instrument to be applied in videotaped psychotherapy sessions during acute and continued/maintained depression treatment. The KERI-D assesses relapse-preventive elements that include both quantitative and qualitative aspects of the related psychotherapeutic process. The main objectives were to 1) assess the reliability of the KERI-D on an item level, 2) determine whether the KERI-D is able to identify relapse-preventive interventions occurring during psychotherapy, 3) explore the factorial structure of content items, 4) investigate associations with clinical outcome data, and 5) assess content validity of the KERI-D as measured by expert ratings.

4.3.3 Methods

Developing the rating material

Developmental steps. The KERI-D was developed by means of the following iterative steps: First, literature was screened for information on relapse-preventive strategies recommended in manuals for clinical practitioners [e.g., 39, 203]. Existing treatment integrity scales were screened [80, 206, 207, e.g., 208]. In addition, experienced psychotherapists were interviewed on how they define relapse prevention and how they implement such strategies in their daily routines [209]. Second, major categories and corresponding items of relapse prevention were derived from theory [39, 176]. By screening six videotaped psychotherapy sessions additional aspects of relapse prevention not yet derived by previous steps were elicited. For this step, the last three sessions of two psychotherapies had been selected randomly from all available videotaped psychotherapies (see section “Assessing the reliability of the KERI-D”). This process resulted in six categories with 183 items. After conceptually overlapping items were condensed and re-reviewed regarding their relevance for relapse-preventive efforts, a preliminary version with five categories and 39 items was prepared.

Third, this preliminary version of the rating scheme was used for pilot ratings by three to six raters. The rating included repeated discussions with members of the research team on

how to adapt and optimize the rating scheme. All decisions were made by consensus. Each revised version was used in multiple rating trials. Agreement between raters was assessed frequently to ensure reliability of the instrument. Highly discordant ratings were discussed by all raters, and the rating manual was revised accordingly and finalized. This process resulted in four categories and 20 items, presented as the KERI-D (**K**odierbogen zur **E**rfassung **R**ückfallprophylaktischer **I**nterventionen bei **D**epression/Coding System to Assess Interventions of Relapse Prevention in Depression) [210]. (A more detailed report in German on the instrument development can be requested from the last author.)

Content of the KERI-D. The four main categories, their corresponding items, the transfer item, and rating procedures are described below. Items of category A to C cover the patient's individual concerns of the past and the future, the implementation of specific interventions and strategies, and potential problems in transforming those in daily routine. Category D contains elements referring explicitly to the end of treatment and to the preparation of the post-treatment phase. Since items in these four categories relate to specific contents covered in the therapies, they are referred to below as "content items". In contrast, the transfer item refers to an overall rating of the whole therapy session and describes how the therapist facilitates the translation from therapy to the patient's daily life after terminating therapy. For the complete rating sheet including all items, see Appendix C and D, p. 210.

Self-care (A). Five items assess the extent to which the patient's individual positive activities and resources are addressed. Sample item: "Specific opportunities and resources for practicing self-care are discussed."

Early warning signs (B). Four items assess to what extent the patient's symptoms are addressed, in terms of recognizing depressive mood adequately when it develops. Sample item: "Specific methods to monitor and recognize early warning signs are discussed."

Triggering events and situations (C). Four items assess to what extent potentially triggering events and situations that may contribute to a relapse are addressed. Sample item: "Specific strategies to prepare for potentially triggering events and situations are discussed."
Termination of therapy and planning next steps (D). Six items assess whether the following issues are discussed: most important findings in therapy, goals in life, continuation treatment options, plans for the future, importance of relapse prevention strategies. Sample item: "The patient's most important findings during therapy and/or achievements are discussed."
Transfer item: This global item measures the extent to which the therapist addresses issues (of categories A to D) in a way that encourages the patient to implement and sustain the skills, knowledge or competences gained in therapy in their daily routine, and continue these efforts over the long-term.

Assessing the reliability of the KERI-D

Psychotherapy sessions. Data were provided by a study conducted in Zurich, Switzerland (NCT01012856), comparing the effectiveness of (CBT) and Exposure-Based Cognitive Therapy (EBCT-R) in patients suffering from an acute episode of unipolar major depressive disorder [211]. The study included 144 outpatients and 28 therapists. Each therapist provided both CBT and EBCT-R. Whereas both treatments had separate treatment manuals, the relapse-preventive section of both manuals was identical. All patients were offered 22 sessions of either CBT or EBCT-R. The therapy sessions analyzed for the current article were selected using the following criteria: Videotapes of the patient's final two therapy sessions (21 and 22) were available in good audio-visual quality. Sessions 21 and 22 were selected because relapse-preventive elements were to be expected in the terminating phase of therapy. To achieve a maximal variance in the implementation of relapse prevention elements, all study therapist with at least one patient were included in the analyses.

Raters and rater training. Three students at Master's level in clinical psychology served for the final rating of 72 therapy sessions. Each rater underwent a one-day training session focused on familiarization with the rating manual and the instrument, followed by independently rating the same four videotaped psychotherapy sessions. The raters achieved a median ICC(2,1) of .70 over all items between each of the three pairs of raters ($ICC_{pair\ 1}$= .88 $ICC_{pair\ 2}$= .70; $ICC_{pair\ 3}$= .67).

Allocation of psychotherapy sessions to raters. We used a balanced incomplete block design [212] for allocating the 72 sessions. Each session was rated by two out of the three available raters in order to determine inter-rater reliability, and each rater coded the same number of sessions with each of the other two raters [205]. Furthermore, the sessions were stratified by an equal number of sessions 21 and 22 as well as CBT and EBCT-R sessions in order to minimize bias of therapy sessions between raters. This resulted in a total of 72 rated sessions from 36 therapies provided by 22 therapists. The mean length of sessions was 55 minutes (session 21) and 54 minutes (session 22).

Rating process[7]. All items are rated on a five-point Likert scale for how much the rater would agree (not at all … thoroughly) that a therapist's behavior was shown during an entire therapy session [213, 214]. For each item, sample dialogues between patient and therapist illustrate the highest possible rating (thoroughly). While watching the therapy session on videotape, the rater is encouraged to take notes, as the final rating is conducted after stopping the video.

Content Validity Index

Content validity of the items was assessed by five content experts determining the Content Validity Index on item level [I-CVI; 215, 216]. Experts were chosen on basis of their

[7] A detailed description of each item and of the rating instructions can be found in the rating manual (in German language), which can be requested by email from the author of this thesis.

experience with research and clinical practice in depression treatment. They had an average of 14 years' experience in research and clinical work. They were asked to rate each item in terms of its relevance to relapse prevention in general and in terms of the item's relevance to each of the four categories (A to D). Relevance was assessed on a four-point ordinal rating scale (1 = not relevant; 2 = major revision needed to be relevant; 3 = relevant and minor alterations needed; 4 = highly relevant).

Analyses

Inter-rater and retest reliabilities were examined by calculating intra-class correlations (ICCs) in a two-way random model ($ICC_{2,2}$), testing for absolute agreement between the two raters or within one rater, respectively. Each rater rated 10% of sessions six months after finishing the first rating [217]. For determining an item's frequency, it was first rated using a five-point Likert scale from 0 (not at all) to 4 (thoroughly). Subsequently, the ratings were dichotomized into "0 = Item did not occur" (formerly "not at all") and "1 = Item occurred" (including the manifestations 1–4 on the former Likert scale). Two-sided *t*-tests on 5%-alpha level were calculated to examine differences between mean scores of items in sessions 21 versus 22. We thus averaged the corresponding two scores for each session and item [207], and most of the items achieved moderate to good ICCs. To estimate a factor structure of items in categories A, B and C, we first merged the scores of sessions 21 and 22, using the higher score of either session 21 or 22. This approach accounts for the fact that some relapse-preventive elements may emerge during session 21, others in the final therapy session, or in both. Then, we determined the number of components by using parallel analysis and the Velicer's Minimum Average Partial (MAP) Test [218]. As both approaches revealed three components for our data set, we specified three factors in the statistic software package SPSS and ran a principal axis analysis (oblimin rotation) to examine factor loadings. As a measure of the internal consistency of the derived factors, Cronbach's alpha was calculated.

Bivariate associations between KERI-D subscales and clinical outcome data (retrieved from the original trial) were determined by calculating Spearman correlations. One analyzed outcome was the self-reported level of depressive symptoms as measured by the Beck Depression Inventory [BDI-II; 144, 219] at posttreatment and at 12-month-follow-up. An additional outcome was diagnosis of a major depressive episode (MDE) at posttreatment, and whether at least one MDE occurred during the 12-month-follow-up. To assess diagnosis of an MDE, we conducted the clinician-rated Structured Clinical Interview [220] at 3-, 6- and 12-month follow-up, and generated a dichotomous variable measuring the occurrence vs non-occurrence of an MDE. Therapeutic alliance as measured by a modified version of the Bern Post-Session Report-Patient Form [221] was analyzed for session 21 and 22. To determine content validity we calculated the content validity index [I-CVI; 215], dividing the number of experts providing a rating of either 3 or 4 by the total number of experts. With five experts or fewer the CVI should be 1.00 for each item to consider it a reasonable representation of the construct.

4.3.4 Results

Reliability of the KERI-D

Table 5 shows the median ICC across all three pairs for each pair of raters. The median ICCs ranged from 0 to .95, with a mean of .69 and a median of .80. The items varied substantially in terms of inter-rater reliability, particularly for the items that occurred infrequently (see table 7). Table 6 shows retest reliabilities for each rater and the median score over all three raters. Median ICCs ranged from 0 to 1, with a mean of .85 and a median of .93. We did not determine a median score for items A2c and B2a since just one rater provided a reliability score (see table 6). For the majority of items the correlations indicate sufficient stability of ratings.

Table 5 *Intra-class correlations for each pair of raters and overall (median)*

Items	Rater 1-2	Rater 1-3	Rater 2-3	Median
Category A: Self-care				
A1a (self-care activities)	.79	.90	.88	.88
A1b (patient resources)	.92	.73	.79	.79
A2a (opportunities practicing self-care)	.55	.85	.35	.55
A2b (difficulties in practicing and maintaining)	.81	.84	.55	.81
A2c (options for monitoring/evaluation)	.00	.72	.00	.00
Category B: Early warning signs				
B1a (early warning signs)	.74	.89	.93	.89
B2a (methods to monitor and recognize)	(-)	.35	.00	.18
B2b (strategies for dealing with it)	.80	.89	.93	.89
B2c (difficulties in implementing)	.00	.62	.26	.26
Category C: Triggering events and situations				
C1a (triggering events and situations)	.94	.81	.88	.88
C2a (strategies to prepare)	.62	.44	.75	.62
C2b (difficulties in implementing)	.54	.65	.53	.54
C2c (symptoms of relapse, emergency kit/plan)	.71	.92	.85	.85
Category D: Termination of therapy and planning next steps				
D1a (findings during therapy/achievements)	.75	.63	.85	.75
D1b (life goals)	.72	.81	.60	.72
D1c (emotions and cognitions on terminating therapy)	.94	.86	.85	.86
D2a (options for contacting therapist after terminating therapy)	.85	.90	.91	.90
D2b (continuing treatment)	.86	.95	.97	.95
D3a (chance of a relapse, significance of relapse prevention)	.46	.77	.64	.64
Transfer item (extent the therapist encourages patient to implement and sustain skills, knowledge, and competencies gained in therapy in daily routine and in the long term)	.60	.80	.85	.80

(-) … ICC could not be calculated as there was no variance between the raters. Each pair of raters coded the same N = 24 sessions; the intra-class correlations should therefore be interpreted with respect to these 24 sessions.

Table 6 *Retest reliabilities for each rater and overall (median)*

Items	Rater 1	Rater 2	Rater 3	Median
Category A: Self-care				
A1a (self-care activities)	.93	.91	.80	.91
A1b (patient resources)	.94	.46	0	.46
A2a (opportunities practicing self-care)	.98	1	.59	.98
A2b (difficulties in practicing and maintaining)	.92	.97	0	.92
A2c (options for monitoring/evaluation)	(-)	1	(-)	- [a]
Category B: Early warning signs				
B1a (early warning signs)	.98	.95	.96	.96
B2a (methods to monitor and recognize)	(-)	(-)	(-)	- [a]
B2b (strategies for dealing with it)	1	.70	.88	.88
B2c (difficulties in implementing)	1	1	0	1
Category C: Triggering events and situations				
C1a (triggering events and situations)	.93	.96	.95	.95
C2a (strategies to prepare)	.96	0	.91	.91
C2b (difficulties in implementing)	1	0	.98	.98
C2c (symptoms of relapse, emergency kit/plan)	1	.89	1	1
Category D: Termination of therapy and planning next steps				
D1a (findings during therapy/achievements)	.94	.93	.91	.93
D1b (life goals)	.98	.89	.98	.98
D1c (emotions and cognitions on terminating therapy)	.89	.75	(-)	.82
D2a (options for contacting therapist after terminating therapy)	0	0	.47	0
D2b (continuing treatment)	1	.82	.85	.85
D3a (chance of a relapse, significance of relapse prevention)	.78	0	.86	.78
Transfer item (extent the therapist encourages patient to implement and sustain skills, knowledge or competences gained in therapy into his/her daily routine and in the long run)	.95	.71	.96	.95

(-) … ICC could not be calculated as there was no variance between the rated scores. [a]*… no median score determined because only one out of three scores was available. N = 5 sessions for each rater.*

Item frequency

Table 7 shows relative frequency rated by each rater individually and the median frequency over all three raters. The median occurrence of items ranged from 2% to 96%, with a mean of 45.8% and a median of 47%. Item frequency ranged widely, with some items being rated to occur in almost every session (e.g., transfer item) and others almost never (e.g., A2c: options for monitoring).

Comparison of sessions 21 and 22

The mean scores ranged from 0.07 to 1.93 in session 21, and from 0.03 to 2.65 in session 22. Four items showed significant differences between the two sessions, with all four session 22 items achieving a higher rating in comparison to 21 (C2c: $t(70) = -2.57$, $p < .05$; D1a: $t(70) = -3.07$, $p < .01$; D1c: $t(70) = -3.00$, $p < .01$; D2a: $t(70) = -3.54$, $p < .01$). As the majority of items did not differ between the two sessions we merged the scores of sessions 21 and 22, yielding a mean of 2.56 and a median of 2.58 for these maximum scores. Figure 17 (see p. 160) shows the frequencies of each possible rating category (0…4) for each of the 20 items and the mean of each item on the Likert scale. At least three of five rating categories were coded by the raters in all 20 items, in 17 of 20 items all of the five rating categories were coded, and in 19 of 20 items the highest possible rating (4 = thoroughly) was coded. This resulted in a considerable variety regarding the total amount of the five different rating categories coded. Also the mean scores of items varied largely, with a minimum of .18 (item B2a) and a maximum of 2.92 (item D1a).

Table 7 *Frequency of occurrence of items (in %)*

Items	Rater 1	Rater 2	Rater 3	Median
Category A: Self-care				
A1a (self-care activities)	75	65	65	65
A1b (patient resources)	65	65	60	65
A2a (opportunities practicing self-care)	63	19	46	46
A2b (difficulties in practicing and maintaining)	50	27	33	33
A2c (options for monitoring/evaluation)	2	2	10	2
Category B: Early warning signs				
B1a (early warning signs)	54	60	60	60
B2a (methods to monitor and recognize)	2	2	15	2
B2b (strategies for dealing with it)	48	46	56	48
B2c (difficulties in implementing)	21	10	31	21
Category C: Triggering events and situations				
C1a (triggering events and situations)	46	71	79	71
C2a (strategies to prepare)	17	44	56	44
C2b (difficulties in implementing)	8	10	27	10
C2c (symptoms of relapse, emergency kit/plan)	25	29	31	29
Category D: Termination of therapy and planning next steps				
D1a (findings during therapy/achievements)	96	79	77	79
D1b (life goals)	46	48	56	48
D1c (emotions and cognitions on terminating therapy)	33	29	23	29
D2a (options for contacting therapist after terminating therapy)	33	67	65	65
D2b (continuing treatment)	40	42	31	40
D3a (chance of a relapse, significance of relapse prevention)	79	50	63	63
Transfer item (extent the therapist encourages patient to implement and sustain skills, knowledge or competences gained in therapy into his/her daily routine and in the long run)	96	79	96	96

Each rater coded N = 48 sessions; the frequency of occurrence should therefore be interpreted with respect to these 48 sessions. Example: Rater 1 coded item A1a in 75% of the 48 sessions. Item A1a was rated overall in 65% of all coded sessions (median).

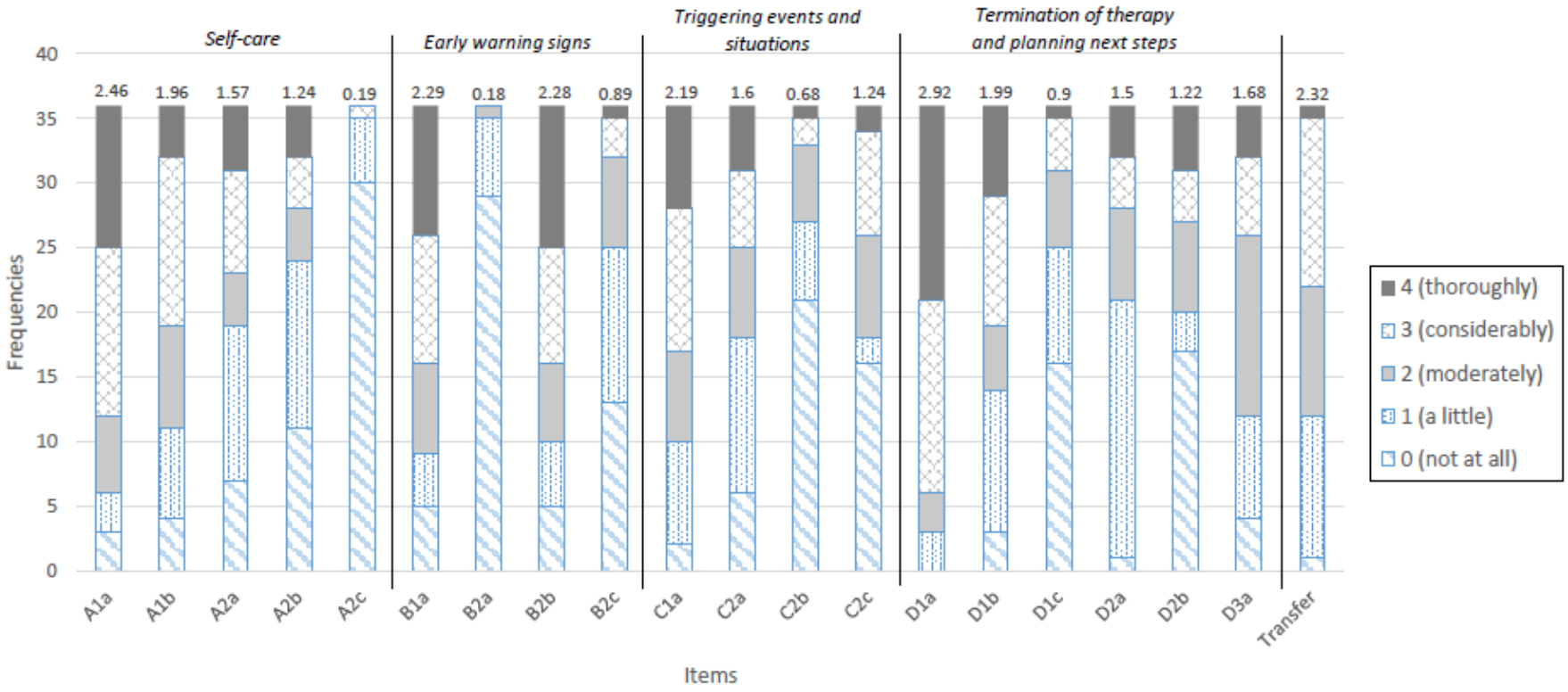

Figure 17. Frequencies and means of KERI-D ratings aggregated over the final two therapy sessions of N = 36 therapies. Frequencies (x-axis) indicate how often each of the five possible rating categories (Likert scale ranging from 0 to 4 with 0 = not at all and 4 = thoroughly)) was observed for each of the 20 items. Merged scores of both sessions 21 and 22 were used. Numbers above each bar indicate the mean score of the item. Items are grouped into four content categories and one transfer item.

First examination of a factor structure

The principal axis analysis revealed factor loadings that corresponded broadly to our theoretical assumptions about three categories (see table 8). All category A items (self-care) loaded on one factor. In addition, items in category B (early warning signs) and C (triggering events and situations) loaded on the assumed factors with one exception. Item C2c (symptoms of relapse, "emergency kit") loaded on the factor composed of category B items. However, all three factors demonstrated good internal consistency in this data set (see table 8), with scores ranging from .75 to .85.

Table 8 *Results of principal axis analysis and internal consistency (N = 36)*

	Factor loadings		
Items	**I**	**II**	**III**
B2b (strategies for dealing with it)	.96		
B2c (difficulties in implementing)	.75		
B1a (early warning signs)	.74		
C2c (symptoms of relapse, emergency kit/plan)	.69		
B2a (methods to monitor and recognize)	.52		
A2a (opportunities practicing self-care)		.88	
A2b (difficulties in practicing and maintaining)		.80	
A1a (self-care activities)		.73	
A2c (options for monitoring/evaluation)		.39	
A1b (patient resources)		.29	
C2a (strategies to prepare)			.92
C2b (difficulties in implementing)			.65
C1a (triggering events and situations)			.54
Cronbach's alpha	.75	.85	.76

Cronbach's alpha is an indicator of internal consistency of the derived factors

The KERI-D subscales and clinical outcome data

Based on results of factor analysis, we integrated item C2c into subscale B, and associated subscales A to C as well as the global Transfer item with clinical outcome data (see table 9). Significant associations between the single KERI-D items were: Higher scores in *triggering events/situations* were positively associated with higher scores in *self-care* and *early warning signs*, and *self-care* was positively associated with the global item *Transfer*. Relating KERI-D to the therapeutic alliance in the last session, a better alliance was associated with higher scores in *early warning signs* and *triggering events/situations.* As expected, higher levels of depressive symptoms at posttreatment and during 12-month-follow-up were associated with occurrence of a major depressive episode (MDE) at both times. No associations between KERI-D subscales and depressive symptoms at posttreatment or during follow-up were found.

Content validity

Thirteen of 19 items had the highest possible CVI rating of 1.00 (i.e., all experts rated an item as relevant); the other six items had a CVI of .80 (i.e., four out of five experts rated an item as relevant). Five of these six items received a rating of 2 (‘major revision needed to be relevant’) on the 4-point ordinal scale. One item (D1c; emotions, cognitions on terminating therapy) was rated by one expert as not relevant at all. However, the other five experts rated this item as highly relevant.

Table 9 *Bivariate associations between scales of the KERI-D and clinical outcome data (n = 25-36)*

	1	2	3	4	5	6	7	8	9	10
1. Subscale A (self-care)	1	.20	.36*	.35*	.12	.09	.04	.07	.19	.06
2. Subscale B (early warning signs)		1	.41*	.33	.06	.10	.08	.25	.23	.45**
3. Subscale C (triggering events/situations)			1	.27	-.15	.03	-.27	.00	.28	.39*
4. Transfer (global item)				1	-.23	-.22	-.26	.08	.33	.28
5. BDI-II (post)					1	.71**	.66**	.56**	-.23	-.22
6. BDI-II (FU)						1	.46*	.67**	-.37	-.21
7. Major depressive episode (post)							1	.56**	-.33	-.33
8. Major depressive episode (FU)								1	-.44*	-.25
9. Therapeutic alliance (session 21)									1	.88**
10. Therapeutic alliance (session 22)										1

*BDI-II = Beck Depression Inventory – second edition. FU = 12-month-follow-up. *p < .05; **p < .01.*

4.3.5 Discussion

Aim of this study was to identify a comprehensive collection of explicit relapse-preventive elements during psychological treatment of depression and, on this basis, to develop an observer-based rating instrument called the KERI-D (**K**odierbogen zur **E**rfassung **R**ückfallprophylaktischer **I**nterventionen bei **D**epression/Coding System to Assess Interventions of Relapse Prevention in Depression). 17 of 20 items showed moderate to good inter-rater reliability, as well as moderate to very good stabilities on retest after six months. Whereas most of the assessed items occurred during the final two sessions of acute therapy, the maximum intensity of the coded behaviors shown by therapists was not very high, indicated by an average of 2.56 of 4 points for maximum scores. Factor analysis revealed three distinct factors (self-care, early warning signs, and triggering events/situations) that corresponded largely with theoretical assumptions noted in relevant treatment manuals for relapse prevention. We did not find any associations of KERI-D subscales with depressive symptoms or the diagnosis of a depressive episode during a 12-month-follow-up. However, better therapeutic alliance during the last session was associated with higher scores in two KERI-D subscales (*early warning signs*, *triggering events/situations*). Finally, experts rated the content validity of the majority of items and categories as clinically and scientifically relevant for relapse prevention.

Category D items and the transfer item were not included in the factor analysis, but served to explore further elements of relapse prevention. Category D items specifically target the discussion of the termination of therapy, assessing both aspects related to the therapy itself (e.g., accomplishments in therapy) and aspects of the post-treatment phase and patient's future (e.g., life goals). Three of these six items occurred more often in the very last session than the penultimate one. Generally, items of this category were rated very frequently, suggesting that

therapists considered these topics highly relevant at the end of therapy. Overall and compared to the content items, the transfer item received rather high ratings, demonstrating that therapists did indeed emphasize the importance of implementing according strategies and of transferring therapy gains to life after ending therapy.

The KERI-D was developed on the basis of theoretical knowledge, clinical conceptions as well as videotaped therapy sessions during cognitive behavioral treatment [211]. Reviewing and stabilizing modified cognitions during treatment can be considered core prognostic factors reducing risk of relapse also after terminating treatment [38], and can be assessed by validated and reliable adherence [e.g., CSPRS; 80] and competence rating scales [e.g., CTS; 81]. In addition to existing measures, the KERI-D has an explicit focus on relapse prevention interventions that aim to prepare the implementation of strategies after terminating treatment. As we consider leading the therapy session towards transferring therapy contents and gains into daily routines mainly as tasks and achievements of the therapist, the KERI-D primarily evaluates therapist behavior, comparable to observer-based instruments assessing treatment integrity [222]. However, it is important to note that so far, the rating of the KERI-D items neither represents a distinct adherence or competence measure [77] for the following reasons:

1) The treatment manual used in the study providing the videotaped psychotherapy sessions to be analyzed [211] did not include recommendations for relapse prevention that were as detailed as we later specified them in the KERI-D. Thus, therapists could not be adherent to the study-specific treatment manual regarding several relapse prevention elements as defined by the KERI-D. However, the current KERI-D intends to address a therapist's adherence regarding the implementation of specific relapse-preventive efforts beyond a specific manual given that several forms of psychotherapy recommend the application of such elements during the final phase of psychological treatment [176, 201–204].

2) Therapist's competence is defined by the way techniques are implemented in a skillful manner [77]. For example, the Cognitive Therapy Scale [CTS; 81] contains two subscales 'general competencies' and 'specific competencies', whereby the latter one includes such aspects as the *choice of adequate strategies* and *adequate implementation of techniques*. These aspects are close to the KERI-D ratings given that higher scores on the KERI-D items imply better implementation of the content the item addresses. However, in the KERI-D the quality of implementation towards sustainability is rated with regard to specific contents (e.g., difficulties in implementing strategies for dealing with early warning signs) and also with regard to time after terminating therapy. This procedure differs from competence rating scales such as the CTS, which focus on the implementation of general techniques during the session (as clarity of communication, resource activation) without focusing on the time after therapy. However, the KERI-D currently includes one global item ('Overall impression of the whole session: Transfer'), which could be considered comparable to the global item of the CTS ('overall rating of competence').

Strengths

We developed an observer-based rating instrument using qualitative and quantitative techniques with additional support from scientific and clinical experts. As relapse prevention is recommended in several forms of psychotherapy [176, e.g., 203] and because the contents of its items is not CBT-specific, the KERI-D may also be used for analyzing therapy sessions from other therapies than CBT. Moreover, the KERI-D can be applied for ratings of end-phase sessions of acute treatment preparing patients for life after terminating therapy, but can also be used for ratings of sessions within continuation and maintenance treatments, which explicitly target the long-term prevention of relapse or recurrence [6]. During the development of the KERI-D, up to six raters rated videotaped psychotherapy sessions. Having trained observers evaluate therapist behavior is considered more objective than relying on

therapist self-reports of the accuracy of delivering the treatment [82] and can be considered a strength of the proposed rating instrument. Furthermore, as 22 therapists contributed data, our analysis covers a wide range of relapse-preventive behaviors. As the psychotherapy sessions used for our ratings originate from a study not explicitly focusing on relapse prevention, therapists could not know that they would be evaluated for relapse-preventive efforts increasing external validity of the instrument and clinical representativity [223].

Limitations

Although the KERI-D showed satisfactory reliability and content validity in its first application, the analyses were based on a small and particular sample of selected psychotherapy sessions. Together with the chosen statistical methods (e.g., explorative factor analysis), only limited conclusions can be drawn. A next step would be to analyze further psychometric properties of the KERI-D referring to a larger sample size, including confirmatory factor analysis and further validation with clinical outcome measures and other (rating) instruments [224]. Generalizability of the reported results may also be limited because the psychotherapies were videotaped as part of an experimental trial with a maximum session number of 22. The resulting characteristics of the sampled psychotherapies could have biased the results with respect to occurrence and intensity of observed behaviors in comparison to therapies in other settings (e.g., time unlimited therapies or therapies focusing specifically on relapse prevention). Furthermore, the three raters of the final rating were also involved in the development of the KERI-D, and were thus familiar with the manual before the official rater training. Consequently, more extensive rater training might be required to validate the instrument by other researchers, considering that the amount of time invested in rater training in other studies varies between 10 and 30 hours [205, 225].

Implications for research and practice

The inclusion of relapse-prevention elements in the last sessions of a psychotherapy is meant to help the patient prepare for the transition from therapy to life post therapy in ways that may reduce the likelihood of relapses. Yet, we found no correlative associations between the current KERI-D subscales and clinical follow-up data (i.e., depressive symptoms or major depressive episode during a 12-month follow-up phase). Investigating longitudinal associations of relapse-prevention elements as assessed by the KERI-D with clinical outcomes in larger samples would promise to give more detailed information about the relevance of particular elements, and may suggest which elements may be integrated into future treatment recommendations. Besides assessing predictive validity of the scale [226], we recommend further studies to address the following issues: First, applying the KERI-D also in continuation and maintenance treatments, as they specifically aim at preventing relapse in the long-run (DGPPN 2015). Second, assessing construct validity [226] by associating the KERI-D with instruments for the assessment of relapse-preventive processes [e.g., CBMT-AS; 206]. Third, investigating the KERI-D with clinical experts as observers [77].

Conclusion

To our knowledge, this is the first instrument that measures specific relapse-prevention elements in psychotherapy by observer ratings. Considering the high relapse rates of formerly depressed patients after a successful acute treatment, an effective relapse prevention is important to maintain gains of therapy. The development of the KERI-D is a first step in defining specific relapse-prevention elements during psychotherapy against depression by providing an instrument that assesses the occurrence and intensity of these elements above and beyond cognitive elements. By this, the KERI-D could make a significant contribution to further investigating the impact of relapse prevention in depression treatment.

5 General discussion

This thesis addresses relapse-preventive efforts of treatments in depressive disorders to sustain remission and recovery in the long-term. As acute treatments are widely investigated already, this thesis set its focus on long-term treatments in terms of continuation and maintenance interventions in individuals being at high risk for relapse and recurrence. It is of further interest whether and to which degree therapists apply relapse-preventive efforts during psychotherapy, which might enhance transfer of therapy gains throughout and beyond depression treatment.

The next chapter will shortly summarize and discuss the main results of each study, alongside with clinical and methodological issues regarding conductance of the study and evaluation and scope of the found results. The subsequent chapters will discuss overall findings gained from this thesis as well as recommendations for future research.

5.1 Summary and discussion of study results

5.1.1 There is limited evidence on continued and maintained pharmacological and psychological treatments for individuals with persistent depression (study 1)

Despite the recommendation of continuation and maintenance treatments for individuals being at high risk of relapse and recurrence of their depression we were able to include only ten studies addressing these treatment phases in persistently depressed patients into the systematic review and meta-analysis. The only result we consistently found was that antidepressant medication (ADM) is superior to placebo regarding the reduction of relapse/recurrence, comparable to results regarding the acute treatment phase in PDD [56, 57]. However, none of these studies provided follow-up data, leaving questions open on long-term effects beyond the termination of ADM treatment. Moreover, two of the five included ADM

studies reported that concomitant treatment was allowed, and that 40% to 60% of their participants received ongoing psychotherapy (in both the ADM and the placebo group). Even though parallel treatment is not necessarily considered biasing the results, the observed individual change is most likely not solely based on ADM (i.e., the study treatment) but also on psychotherapy (i.e., non-study treatment) in the respective two studies. This may highlight the relevance of combined psychological and pharmacological long-term treatment in persistently depressed individuals. Only three studies provided data on psychotherapeutic treatments, and these studies differed markedly in frequency and form of provided psychotherapy, and also in analyzed outcomes. However, we assume that individuals with PDD might benefit from continued and/or maintained psychotherapy, but due to the limited amount of analyzed studies this assumption cannot be confirmed meta-analytically.

Several methodological issues arose during conducting this meta-analysis, which might be considered for prospective reviews and meta-analyses focusing on relapse-preventive efforts and long-term treatments. *First* of all, some studies addressed the problem of missing data with the LOCF (last observation carrying forward) method, which assumes stability of data over time [164]. With respect to high relapse and recurrence rates in depressive disorders [1] we consider this method inadequate and potentially overestimating the proposed long-term effectiveness of treatments. The CONSORT guidelines recommend using more than one imputation analysis set for studies in which non-compliance (e.g., loss to follow-up) is an issue [227]. This means that different approaches for imputing missing data in long-term trials should be applied and presented in publications in order to assess the influence on effectiveness outcomes of each imputation method [228].

Second, for the majority of addressed comparisons we found marked heterogeneity between trials, which raises the question if meta-analysis is the adequate method for summarizing data originating from studies which differ greatly in kind and quality of applied methods [229]. The so-called ‘garbage in, garbage out’ problem assumes that meta-analyses

can hardly correct for low quality of primary studies, resulting in low quality of overall effects computed by meta-analyses. By applying sensitivity analyses we accounted for differences in trials excluding those with high risk of bias in one or several domains. However, due to the generally limited number of included studies this method was somewhat obsolete for our analyses, as it sometimes resulted in only one remaining study of high quality. Improving the significance of a meta-analyses implies improvement in conducting primary studies [230], which can be supported by guidelines as the CONSORT statement [231], which define a clear reporting procedure when conducting randomized-controlled trials (RCTs).

Third, we defined rather strict criteria for including relevant studies. More specifically, we required the studies to apply clear response and remission criteria for the patients who are considered eligible for entering continuation and maintenance treatment, and we included only studies treating PDD patients or reporting data on that population. Consequently, we excluded studies [139, 197, 200, 232, 233] that address long-term interventions for individuals who had been suffering from depression for many years because the studies failed to clearly report on required data as explained above. Thus, we recommend a consistent use and implementation of definitions (e.g., response, remission, continuation, maintenance) in further studies to better specify treatment options and to better estimate treatment effects.

Fourth, this leads to the discussion if there is actually a need for this clear differentiation between acute, continuation and maintenance treatments, and also between PDD and recurrent depression with full inter-episode recovery. Do therapists treat recurrently depressed individuals, who have been affected for ten years differently from those individuals who have been suffering from PDD for ten years? And is it more reasonable for all individuals being at high risk to receive long-term care, or for reception of a specific care to depend on response and remission status? Even though expressed quite offhand, this shall illustrate that strict definitions in research might not always address the needs of complex mental health care adequately [230]. For conducting a further meta-analysis, I would

recommend to include studies addressing long-term interventions for depressed individuals being at high risk for relapse and recurrence, followed by several subgroup analyses targeting the above mentioned issues (e.g., diagnostic subgroup, treatment phase, response/remission status).

Fifth, meta-analyses usually target specific stand-alone interventions because likelihood of homogenous trials increases, and consequently, it is possible to draw clear conclusions on direction and causes of effects. With respect to individuals suffering from chronic mental illness, it might be questioned if a complex treatment concept including several providers and treatment options might be preferred over single approaches [234]. Unfortunately, such integrative treatment concepts for chronic conditions [235, 236] are rarely investigated as testing the effectiveness of complex interventions including various treatment components and providers is associated with methodological challenges [237]. For instance, domains as 'random sequence generation', 'allocation concealment', 'blinding of participants and personnel', 'incomplete outcome data', implementation of which is required for a well-done RCT [153], can hardly be managed within complex interventions. Additionally, clinical heterogeneity regarding population, intervention and implementation hamper a meaningful and valid synthesis of data [238]. Thus, studies addressing such concepts might be more often excluded by reviews/meta-analyses, although mental health care provided by a team of practitioners including several treatment concepts might increase likelihood that individuals being at high risk are constantly monitored and treated in the long-term.

Regarding the aim of this thesis we assume that persistently depressed patients benefit from continued and maintained ADM, and that they might benefit from psychotherapy as well. However, the effectiveness of the examined treatments can be ascertained for as long as these treatments are provided. Conclusions on long-term effectiveness after termination of continuation and maintenance treatments cannot be drawn, and studies are advised to collect follow-up data and to handle missing data accordingly. Additionally, there is a clear need for

conducting studies addressing long-term care for PDD patients, especially targeting psychological interventions and their combination with ADM. Several methodological and clinical issues might be considered for further studies to improve number and quality of investigations, and to consequently widen the scope of study results. With respect to the limited number of long-term psychotherapy studies investigating high-risk individuals, we developed a low-intensity telephone-based continuation therapy for recurrently and persistently depressed individuals who had responded to acute psychotherapy. Within a pilot study we assessed feasibility and acceptance of the new components of this intervention to evaluate which components need improvement, and to later run a larger randomized-controlled trial addressing the effectiveness of this intervention.

5.1.2 A telephone-based continuation psychotherapy for depressed individuals at high risk for relapse is feasible under specific conditions (study 2)

Use of the medium telephone was predominantly associated with well-known advantages as low-threshold access with personal contact, omission of journey to therapy (which is especially relevant for individuals living in rural areas or for those being physically impaired), and a more flexible integration of therapy into everyday life including job and family responsibilities [113, 117]. Moreover, both patients and therapists perceived the development and maintenance of a sound therapeutic relationship comparable to face-to-face settings, as has also been described in other studies [115, 185]. The most relevant issue discussed during the interviews was the implementation of a continuation therapy concept, which was considered to be dependent on several preconditions including success of previous acute therapy, time frame of sessions and a clear treatment plan, especially if patient and therapist are unfamiliar at the beginning of continuation therapy. The decision of whether or not a patient can enter a continuation therapy should take into account level of depressive

symptoms as well as availability of effective coping strategies. Although a 30 minutes phone session each month was perceived feasible if both participant and therapist applied a high level of prioritizing of concerns, a 50 minutes setting was selected as first choice. Longer intervals between sessions (e.g., one month) were perceived as challenging (compared to acute phase settings), but also valued by participants, as this encouraged them to cope with everyday life on their own again. In summary, we assume that the above mentioned preconditions should be ensured in the first instance, and that the medium telephone might facilitate access to this intervention.

However, whether change in health status of our participants can be attributed to elements of the intervention or other factors remains unclear due to lack of a control group and a small sample size. A randomized-controlled trial (RCT) organized by the same department which conducted this pilot study investigates the effectiveness of the telephone-based continuation therapy compared to treatment as usual ('Natel'; NCT03219879), optimized and adapted based on results of this pilot study. For the ongoing RCT the following setting was implemented: eight phone sessions lasting approximately 50 minutes within six months, the acute phase therapist ideally provides continuation therapy as well, each session and the entire treatment are more structured in terms of using working sheets, stronger focus on patient's skills and a constant reference to these skills throughout therapy.

Besides recommendations regarding this specific intervention, the following sections will discuss overall issues, which might be considered when providing relapse-preventive long-term treatments for high-risk individuals. RCTs enable researchers to estimate the effect of one intervention compared to other interventions or no intervention at all. However, most studies do not account for a possible misfit between needs and expectations of a patient and the provided intervention [117]. For instance, we had one participant in the pilot study who reported to not have benefitted from our intervention at all. During the interview, it emerged that this participant had expected to get further intense acute treatment once per week and

preferably in a face-to-face setting. Moreover, this participant reported to have had actually no time for a therapy due to family and job responsibilities, which resulted in phone sessions occasionally conducted while on the train. It is understandable that this participant did not benefit from this intervention because her expectations regarding the intervention could not be met by the intervention we intended to provide. As a consequence, we recommend to clearly discuss opportunities and boundaries of a continuation therapy, as well as differences and common features between face-to-face and telephone settings. Additionally, motivation of a patient to continue treatment even though remission has been achieved should be enquired.

Motivational aspects influencing entering therapy and will to change are already focus of scientific inquiry and known to predict therapy outcome [239]. Motivational and other processes (within the patient, but also in the environment), which might influence whether chronic patients continue psychotherapy or not, are unknown, yet. This might be of clinical relevance as chronic conditions are likely to need long-term or even lifetime treatment, and sometimes without expectation of entire cure. In clinical routine care, motivational interviewing and psycho-educational interventions are implemented trying to improve adherence to treatment, especially to taking medication [240]. Most research focuses on adherence to medication because pharmacological treatments of severe psychiatric disorders are, depending on the specific diagnosis, commonly first choice treatment. Unfortunately, the WHO reported that even in developed countries only 50% of individuals suffering from chronic diseases (including depression) adhere to treatment recommendations regarding long-term therapy [241]. Even though the mechanisms of why depressed patients do not follow treatment advice are still unclear and might be related to the illness itself [242], it is assumed that patients make their decision by balancing perceived risks against benefits based on available information [243]. Although patients tend to associate medication with harms [32], there is still limited research if psychological interventions might lead to any harms [244]. Consequently, investigating negative outcomes of psychotherapy as well as the patients´

beliefs regarding such negative outcomes could be focus of future research, in combination with testing the impact on continuing or quitting long-term therapy.

Our therapists mentioned that participating patients had been probably more motivated compared to patients in common routine care settings. Also, the two therapists themselves had an affiliation to the conducting department, and might have been more motivated compared to routine care therapists. Both aspects reflect that the population investigated in controlled study settings and routine health care settings differ [245]. Participating in a RCT is usually associated with receiving therapy free of any charges, and therapists receive time, money and frequent supervision from the study team. By contrast, routine care therapists adhere to the system they work in, e.g., treatment options and procedures are clearly defined by the hospital or praxis. Providing or organizing care, which exceeds the care provided by the system requires individual motivation and belief in other treatment concepts. Our pilot study was a mixture of settings in some way. We intended for routine care providers to refer eligible patients to our study, so that they could receive continuation therapy, which was provided by our study therapists who had a scientific affiliation. Unfortunately, we had difficulties recruiting eligible patients as only one hospital referred patients to our intervention. Although recruiting is a common problem in community-based mental health research [246], we can only speculate about why the majority of providers who had previously agreed to participate, did not participate in the end.

Mason and colleagues [246] identified several barriers including concern about protecting the patient and impact on the relationship between therapist and patient. We received feedback from providers that they do not believe that their patients would continue psychotherapy over telephone with an unfamiliar therapist. Thus, it is likely that such providers did not offer our intervention to their patients, as their own clinical attitude did not correspond with the format of our intervention. The ongoing RCT did incorporate this concern by deploying acute phase therapists also for the subsequent continuation therapy, i.e.,

ensuring continuous therapists. However, there might be other barriers regarding recruitment, which could be addressed by further research. With respect to our pilot study, knowing about specific barriers would help to optimize elements associated with treatment delivery, i.e., which elements should be included that patients actually have access to and participate in a study or routine care intervention in a specific health care system: What kind of patient needs this intervention? Is this system (insurances, hospitals, therapists) able and willing to provide this intervention? Who covers the costs for this intervention?

Regarding the aim of this thesis we assume that a telephone-based continuation therapy for depressed individuals at high risk for relapse might contribute to sustained remission in the long-term. However, this assumption is based on results of a small pilot study so far, and needs further investigation. Moreover, encouraging providers and patients to participate in this intervention was challenging, and further investigation of the reasons for these recruiting difficulties is needed. Exploring factors as motivation and beliefs regarding long-term treatment would be a valuable research issue to test a potential impact on a patient's decision on continuing or quitting therapy. Besides motivation and beliefs there are further treatment elements, which are discussed to have an impact on treatment outcomes, as level of depressive symptoms and dropout rates. Whilst the majority of studies investigated cognitive processes as possible mechanisms in relapse prevention so far, we were interested in whether or not further relapse-preventive efforts are observable during psychotherapy. We developed an observer-based rating instrument, which targets the transition of therapy gains into the patient's everyday life throughout and beyond termination of treatment, and analyzed this new instrument for its psychometric properties.

5.1.3 Therapists show relapse-preventive efforts during psychotherapy which exceed core concepts of cognitive-behavioral therapies (study 3)

We could show that therapists apply relapse-preventive efforts during the end of acute psychotherapy, which exceed elements covered by existing adherence and competence scales. Items of the newly developed "KERI-D" (**K**odierbogen zur **E**rfassung **R**ückfallprophylaktischer **I**nterventionen bei **D**epression/Coding System to Assess Interventions of Relapse Prevention in Depression) show moderate to good inter-rater and retest reliabilities, and three subscales emerged during analyses. First evidence on content validity could also be demonstrated. However, the KERI-D showed no correlative associations with clinical outcome data (depressive symptoms; occurrence of a depressive episode) during a 12-month-follow-up. Thus, the proposed instrument contributes to defining relapse-preventive efforts during psychotherapy, but needs further conceptual development and, moreover, statistical investigation by applying longitudinal models to explore whether such relapse-preventive elements actually predict relapse and recurrence in the long-term. These findings have to be interpreted taking several methodological and clinical issues into account:

First, the observed therapists were not trained specifically in relapse-preventive efforts but rather focused on being adherent to the treatment manual. This might be a strength of this study as it allowed us to observe relapse-preventive efforts which a therapist might also show in routine care settings. As a consequence we might get a deeper understanding of what relapse prevention actually is, or, in other words, what elements the concept of relapse prevention is composed of. Although 'relapse prevention' is a common term used in clinical practice, there is no measure or common guideline available, which clearly defines elements of this concept.

Second, trials investigating relapse prevention consider the core concepts of the delivered treatment to be the mechanism that lead to patient change, e.g., change in dysfunctional beliefs during CBT might lead to a decrease of depressive symptoms [101]. However, such processes are measured within the treatment period and it remains unclear how enduring such change in core concepts is, and how the patient manages to sustain such therapy achievements also beyond the termination of therapy. The KERI-D tries to assess how therapists encourage the patient to sustain therapy gains throughout and beyond therapy. However, we only assessed the therapist's perspective. As clinical outcome data such as rates of relapse and recurrence are usually applied as indicators for predictive validity, it would be valuable to assess what kind of strategies and elements of therapy *patients* can specify by the end of therapy. By measuring only the therapist's behavior we do not know what relapse-preventive components the patient actually mastered or internalized. The patient´s level of achievement or internalization might be another factor for predicting relapse (compared to therapist's initiations of relapse-preventive efforts), for instance with the help of a self-report questionnaire measuring the patient's extent of available relapse-preventive strategies and their usefulness, importance and practicability in everyday life. Moreover, the association between therapist's initiation of relapse-preventive efforts and patient's level of relapse-preventive achievements would be of high interest for exploring the therapist's influence on relapse prevention, which in turn would have influence on a possible integration of relapse-preventive elements into treatment manuals.

Third, the extent to which the KERI-D overlaps with existing adherence and competence scales is of interest for further development of the KERI-D. For instance, the Cognitive-Behavioral Maintenance Therapy—Adherence Scale (CBMT-AS) [206] is applied during a psychotherapeutic maintenance therapy intending to prevent relapse and recurrence in the long-term. Whilst the CBMT-AS mostly contains items regarding core mechanisms of CBT, the KERI-D explicitly focuses on further relapse-preventive efforts (as cognitive

elements are already covered by existing instruments as the CBMT-AS). Thus, a combination of both cognitive elements (‘reviewing dysfunctional beliefs’) and more general relapse-preventive efforts (‘strategies to prepare for triggering events and situations’) might enrich a tool to broadly cover the concept of relapse prevention, especially if applied in cognitive-behavioral interventions. On the other hand, the KERI-D might differ from existing adherence and competence scales as it does not rely on or refer to a specific orientation in psychotherapy. The KERI-D in its current form may be applied in all forms of psychotherapy as it tries to assess elements, which focus on the transfer from therapy achievements to time after therapy, irrespective of contents of these achievements. And we consider this focus to be highly relevant in depressive disorders, as therapy should not only intend to decrease depressive symptoms in the short-term, but moreover to enable the patient to frequently and independently use and adapt achieved strategies to maintain well-being in the long-term. In other words, one part of relapse prevention differs between psychotherapy orientations, namely the proposed mechanisms that lead to symptom change (which are usually defined by the core theoretical concept of this orientation). The other part, which is intended to be covered by the KERI-D, might be considered a more universal approach to relapse prevention, as it focuses on the process and transfer of therapy gains, and should therefore be relevant to all forms of psychotherapy.

Fourth, we introduced the KERI-D to be applicable in all three treatment phases. However, initial development and investigation of psychometric properties as presented in study 3 were conducted with videotaped psychotherapy sessions retrieved from last sessions of acute phase therapy. In a next step validation with data from continuation and maintenance therapies would be of interest for possible extension of the current KERI-D including aspects, which were not apparent within previous developmental steps.

Finally, the KERI-D aims to assess relapse-preventive interventions as declared by its name. However, we found no associations with clinical outcome data (depressive symptoms;

occurrence of a depressive episode) during a 12-month-follow-up, yet. There are several methodological issues conceivable for this result. We analyzed a rather small sample of psychotherapy sessions (N = 36) of the availa ble data pool (N = 144), and we did not randomize these sessions but selected video material with regard to structural circumstances (e.g., availability of sessions 21 and 22 in good quality). Additionally, clinical outcome data at 12-month-follow-up was not available from all 36 participants. The combination of these circumstances might diminish likelihood of meaningful results.

On the other hand, one could discuss whether the KERI-D should be actually able to predict change in depressive symptoms or occurrence of a depressive episode during follow-up. We do not assume that elements measured with the KERI-D are the only responsible therapy elements for improvement or deterioration of mental health status. Elements such as working on dysfunctional attitudes and negative (automatic) thoughts, mindfulness skills, attributional style, rumination, and therapeutic alliance were found to have an influence on patient's symptom change [53]. Moreover, as outlined above, the KERI-D assesses therapist's initiation of relapse-preventive efforts. A measure, which assesses internalized relapse-preventive strategies, which are actually implemented by the patient, might be a better indicator for predicting relapse during follow-up. Despite several research attempts, previous evidence regarding proposed mechanisms of change is evaluated as weak due to methodological issues [53]. Moreover, also studies addressing the association between reliable and valid adherence and competence scales and clinical outcome data cannot present conclusive results [79]. Thus, in future analyses the individual influence of each of these elements as well as the combination of all of these proposed mechanisms could be investigated with regard to change in patient's health status during and beyond treatment.

Regarding the aim of this thesis we conclude that therapists do encourage patients to transfer therapy gains to life after termination of treatment, and that therapists differ in the degree they apply these relapse-preventive efforts. Whether or not those behaviors are

actually relapse-preventive could not be established in this study and needs further investigation by applying longitudinal models in larger samples. Moreover, assessing the patient's perspective on relapse-preventive achievements might give deeper insight into the therapeutic concept of relapse prevention. This study made an attempt to define the concept and elements of relapse prevention that target other components beyond core mechanisms of therapy orientations. We consider this approach meaningful as research of the last decades showed that psychotherapy of any form is effective, but relapse rates tend to be high, in all forms of psychotherapy. Thus, therapy elements, irrespective of the specific form of psychotherapy, might help to define how therapists can enhance the implementation of therapy gains into the patient's everyday life, and by this, reduce risk for relapse and recurrence in the long-term.

5.2 Overall discussion

Previous research developed and investigated several psychological and pharmacological interventions for individuals suffering from depressive disorders. Despite these efforts, relapse and recurrence rates tend to be high, especially in recurrently and persistently depressed individuals. This thesis addresses this situation by conducting three studies that focus on long-term effectiveness of interventions in different treatment phases for high-risk individuals. The systematic review/meta-analysis (*study 1*) showed that continued and maintained antidepressant medication is effective in persistently depressed individuals for as long as medication is provided, that psychological interventions might be effective, and that further studies addressing long-term psychotherapy are needed. *Study 2* showed that continued psychotherapy delivered by telephone is feasible and accepted in high-risk individuals if several preconditions, such as level of depressive symptoms, availability of coping strategies and attitude towards telephone therapy, are ensured. Finally, specific

elements of psychotherapy that might be relapse-preventive throughout and beyond treatment were analyzed in *study 3*, showing that therapists try to enhance the transfer of therapy gains into the patients' everyday life.

Regarding relapse-preventive efforts to sustain long-term remission, this thesis concludes that research provides several attempts to avoid relapse and recurrence, but that conclusive evidence on the effectiveness of these interventions is limited. We outlined that acute phase treatments are effective, but rather in the short-term. Follow-up data exceeding one year post-treatment are rarely reported, which is considered inadequate as studies show that relapse and recurrence rates rise up to 54% within two years following acute treatment [12]. Everyone (patient, provider, system) wishes a short-term therapy to be effective and that the patient quickly returns to a functional level. But facing high relapse and recurrence rates even after successful acute therapy, long-term or even lifetime treatments might be a pessimistic approach, but maybe also the more realistic one for severe depression. The "revolving-door-patient" is an observed phenomenon describing that patients with chronic severe mental illness are discharged from the hospital after acute therapy to be admitted to hospital again sooner or later, multiple times [247]. Whether those patients do not receive adequate inpatient treatment, or if they receive no adequate care following inpatient treatment, is unclear. This thesis sets a strong focus on the latter explanation, especially when referring to persistently or recurrently depressed patients. Whilst providing several short-term treatments with intervals of (more or less) well-being in-between is one way of care, the question is whether this treatment concept corresponds to the needs of a chronically impaired patient. This thesis assumes that long-term care in terms of continuation and maintenance treatments might be the more appropriate way of approaching the recurrent and persistent character of depressive disorders. Such treatments involve continuous monitoring of the patient's symptoms, and reviewing and consolidating achievements of previous therapies.

This concept of care might be able to recognize a patient's deterioration before a full depressive episode occurs, potentially minimizing rates of re-hospitalizations.

This thesis shows that well-investigated continuation and maintenance treatment studies for persistent depressed individuals are rare, and that psychological interventions are overshadowed by research on antidepressants. It can be assumed that this situation in research reflects the current routine care situation, in regard to preference of medication but also in regard to a preference for providing short-term treatments. As the body of previous research found high relapse and recurrence rates even after successful acute therapy, researchers and health care systems might reconsider their current treatment concepts, and considering a long-term treatment perspective for future research. Piloting a telephone-based continuation therapy for high-risk individuals aimed at contributing to this long-term perspective, offering patients who had previously terminated acute therapy a further six months of support. Patients highlighted the value of such a continuation therapy to get further support following acute therapy, underlining the patients' needs and wishes for low-intensity continued care. The effectiveness of this intervention is under current scientific investigation within a RCT conducted in Switzerland and Germany, contributing to the currently limited evidence regarding long-term treatments. With respect to addressing depressed individuals who are at high risk for relapse and recurrence, one could discuss whether six months of continued care including eight therapeutic contacts is sufficient. The dose-effect relationship in psychotherapy mostly refers to the number of sessions needed to observe clinically relevant change in patients, combined with the frequency in which the sessions are provided. Whilst there is still open discussion if number of sessions is a relevant factor, evidence suggests that a higher frequency is associated with steeper recovery curves (e.g., two sessions per week is more effective than one session per week) [4, 248]. Previous evidence is based on acute phase therapies, thus analyses of therapeutic 'dose' in long-term therapies would be of high interest

for patients, providers and policy makers. This thesis addresses this topic, but cannot present any conclusive long-term results beyond treatment termination.

This thesis also explored in more detail which elements of psychotherapy might enhance therapy achievements in terms of relapse prevention. We were able to observe a variety of therapist-initiated efforts, which we consider relevant for long-term relapse prevention from a theoretical and clinical perspective. However, we could not prove any statistical associations between observed relapse-preventive efforts and course of depressive symptoms during a one-year-follow-up, yet. Thus, this thesis contributes to the perspective that therapists should continuously make a link between therapy achievements in-session and their transfer into everyday life, potentially enhancing the durability of therapy gains.

Results from the presented studies indicate that psychotherapeutic long-term relapse-preventive interventions for high-risk patients are rarely investigated or reported, and might also be less often provided in clinical practice compared to acute treatments. Whilst pharmacological interventions are often prescribed as long-term therapy and much more frequently investigated in studies, especially patients with chronic conditions tend to quit medication [241]. It remains unclear why, compared to pharmacological studies, only few studies address psychological long-term interventions, even though they are preferred by patients [32]. Pharmacological studies might be funded more often due to connections to the pharmaceutical industry, and providing antidepressant medication is probably less time-intensive for both therapist and patient. By contrast, conducting psychotherapy research itself might be more cost-intensive, and involving in psychotherapy requires a patient's motivation and time, and moreover, his/her will to change behavior. Moreover, whilst medication is commonly covered by health insurances, psychotherapy is often limited in coverage, and sometimes even not reimbursed at all by insurances. This situation is alarming with respect to reported long-term cost-effectiveness of psychotherapy, especially in patients with severe chronic conditions [249].

Besides discussions about the system's financial resources we should also focus on facilitating access to treatment. Even though clinical guidelines include detailed recommendations of state-of-the art treatments for individuals with severe mental health problems, only between 25% and 40% receive specific mental health care [250, 251]. One part of this thesis tried to address a potential improvement of access by delivering a psychotherapeutic intervention over telephone. This mode of delivery is associated with a low-threshold and flexible access [110] to treatment which shows comparable effects to face-to-face acute treatments [113]. Both participants and therapists of our study perceived this medium as especially adequate for the continuation treatment phase, as reasons for the development and maintenance of their depression were already discussed in detail during the acute phase treatment. Continued monitoring within a less frequent setting was assumed to be feasible by telephone, including advantages as outlined above. Whether or not this intervention is effective and whether or not the medium telephone can improve access to long-term treatment cannot be answered by this thesis, and needs further investigation. But, including remote technologies (e.g., internet, telephone, mobile phone) into mental health care in times of their general availability might facilitate access to psychotherapy for individuals showing preference for such type of treatment delivery.

Summarized, the long-term effectiveness of relapse-preventive efforts for the treatment of depressive disorders is inconclusive especially with regard to psychological interventions. Kind and 'dose' of intervention as well as mechanisms that lead to long-lasting effects remain unclear even though several research attempts exist. One recent work summarizes the achievements of four decades of psychotherapy research in adult depression [4], and concludes that future research should not develop any new psychotherapies for depression. Instead, research should aim to reduce burden of disease by focusing more on relapse prevention and optimizing treatments for chronic and treatment-resistant depression [4]. This thesis agrees with this assumption, and tries to contribute to this research field by

investigating the long-term effectiveness of treatments for individuals at high risk for relapse and recurrence. The following chapter will outline several aspects of current research practice, discussing potential adaptations and recommendations for future research.

5.3 Outlook and concluding remarks

This thesis outlined the need for relapse-preventive efforts for depressed individuals with a high risk of relapse and recurrence, and the limited availability of studies addressing this topic comprehensively. These available studies on long-term care and its effectiveness vary in applied methods and results, leaving open the question whether or not one method or intervention is 'better' than another, and consequently, in which way long-term studies should be ideally conducted. First of all, in research we are confronted with several terms and definitions specifying the population we can treat, observe and analyze. For instance, patients should only enter a continuation treatment phase in case of partial response or remission [8]. In this regard, three aspects are meaningful to discuss. 1) The range between responding to a treatment and remitting with treatment is large, questioning the precision of indication for a continuation treatment. 2) To assess response and remission requires pre-/post data of a patient, and the regular use of psychometric scales in clinical routine care is considered an exception [252]. 3) Usually, studies define a specific number of sessions a patient receives during a specific time frame (e.g., 16 sessions of CBT during 16 weeks of acute treatment), and only those patients responding or remitting during this period enter continuation treatment and only that data is reported. Which patients do improve within 16 weeks and which not, i.e., whose data is reported?

Summarized, even though a clear definition of which patients should enter continued care is available, the consistent implementation of this definition is in question. Studies indicate that patients who clinically remitted during treatment have better outcomes (e.g.,

fewer relapses/recurrences, lower risk of a chronic course of their disease) compared to patients who 'only' responded to treatment [252]. Thus, research might take this into account by requiring remission by the end of acute treatment to ensure that patients are able to continue treatment in another setting. This also indicates that studies might consider not only to predefine a specific number of sessions, but by contrast, to treat until remission. Then, whether or not a patient needs 16 or 30 sessions of CBT to remit could be considered within further analyses. Such a procedure would allow to treat the variety of depressed subjects (especially those with severe forms of depression), and to take the individual course of the disease and needs of a specific patient into account. Obviously, the same applies for the health care system: funding treatment as long as it is needed might be a better approach than funding a defined maximum of sessions. This requires a consistent and feasible application of rating scales to measure remission status. Several reliable and validated clinician-rated and self-report instruments exist (e.g., Hamilton-Rating-Scale, Beck Depression Inventory) [253], but their use in clinical routine care is often associated with limited time to administer those instruments properly [252]. Research might respond to this situation by investigating strategies and systems to better implement such instruments into clinical routine care.

Response, remission, relapse, and recurrence are typical outcomes of interest in depression studies, and although studies and routine care differ in applying and measuring these outcomes, they are state-of-the-art in research. However, besides level of depression severity other outcomes should be acknowledged. We highlighted the relevance of coping skills and depression self-management, which could be further indicators for whether continuation and maintenance treatment is indicated or not, and for whether a patient is prepared to handle critical concerns on his own. Although self-report instruments assessing level of coping during and after treatment exist [182, 192, 193], they are rarely used (or reported) in studies.

By contrast, assessing quality of life is far more integrated into current studies as a secondary outcome, and underlines that patients benefit from psychotherapy not only in terms of a reduction of symptoms, but also in terms of additional outcomes such as quality of personal and work-related relationships, level of comfort and engagement in activities [254]. Especially for severe forms of depression, in which absence or low- levels of depression might not be achieved over lifetime, interventions which increase quality of life might be relevant and beneficial. With respect to quality of life and well-being, some researchers address so-called 'well and unwell weeks' during follow-up periods [255]. Such continuous measures account for fluctuation of symptoms over time, which do not have to lead to relapse or recurrence, but give insight into the health status of an individual. Such long-term measures can be facilitated by use of remote technologies, e.g., monitoring of symptoms with the help of mobile phones to enhance relapse prevention [256].

To conclude, this thesis reported on current evidence regarding relapse-preventive efforts for depressive disorders, underlining the need for continuous long-term care for individuals being at high risk for relapse and recurrence, and the need for enhancing the transfer of therapy gains into the patient's everyday life. Although several attempts had been made during the last decades, prevalence and burden of depression remain high, persistent and recurrent conditions receive little attention, long-term effectiveness of available treatments is questionable, and in addition to this, a greater part of affected people have no access to adequate mental health care. Relapse-preventive efforts can be realized in different forms and during several treatment phases, by enhancing transfer from therapy to time after therapy, and by providing continuation and maintenance treatments. Whether or not these attempts prove effective in reducing relapse and recurrence in the long-term should be focus of future research. Moreover, including remote technologies as telephone, mobile phones and the Internet can enhance access to treatment and might increase likelihood that individuals actually involve in and adhere to long-term therapy. To decide whether and which technology

should be applied, several aspects have to be taken into account, such as level of impairment, attitude towards delivery options and further personal circumstances of a patient.

Researchers as well as stakeholders within the health care system should reconsider their perspectives on available treatment concepts. Stand-alone short-term interventions might be straightforward to investigate and might be affordable at first glance, but might also lead to increasing numbers of "revolving-door-patients" and repeated treatments. Continuous long-term care, which includes frequent monitoring and reviewing of relapse prevention tools over a specific (yet undefined) time span, might appear cost-intensive. On the other side, it may prevent relapse and recurrence by early detection of deterioration and adequate intervening, potentially minimizing burden of disease and enhancing (guided) self-management of depression. Those processes should be implemented with respect to the patient's everyday life circumstances, enhancing transfer from therapy to life after therapy.

The terms 'long-term care' or 'chronic conditions' might imply that depressed individuals at high risk are treatment resistant or need lifetime care, which is accurate in some cases. For the majority of affected individuals it implies that more and longer treatment might be needed, and that the health care system should encourage such individuals to involve in and remain in treatment and to integrate therapy achievements into their lives. Researchers are encouraged to take over this perspective by investigating interventions that prevent relapse and recurrence in the long-term, and applying methods and analyses that address this perspective.

Appendix

A – Search syntax of electronic searches

1. Description of the Cochrane Common Mental Disorders Specialized Register (CCMD-CTR)

The Cochrane Common Mental Disorders Group maintains a specialized register of randomized controlled trials the CCMD-CTR. This register contains over 39,000 reference records (reports of RCTs) for depression, anxiety and other common mental disorders. A percentage of the reference records have been tagged to 12,500 individual, PICO coded study records (with coding based on the EU-Psi coding manual). Reports of trials for inclusion in the register are collated from (weekly), generic searches of MEDLINE, EMBASE and PsycINFO, quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL) and review specific searches of additional databases. Reports of trials are also sourced from international trial registries, drug companies, the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses. Details of CCMD's core search strategies can be found on the Group's website.

2. OVID PsycINFO will be searched using the following terms:

[Condition]
1. (chronic* depress*).ti,ab,id.
2. (double depress*).ti,ab,id.
3. DYSTHYMIC DISORDER/
4. MAJOR DEPRESSION/ and ("CHRONICITY (Disorders)"/ or CHRONIC ILLNESS/)
5. (dysthymi*).ti,ab,id.
6. RECURRENT DEPRESSION/
7. (depress* adj2 recurr*).ti,ab,id.
8. persistent depressive disorder.ti,ab,id.
9. or/1-8
[Maintenance]
10. MAINTENANCE THERAPY/
11. (maintenance or maintained).ti,ab,id.
12. continuation.ti,ab,id.
13. (stable or stabilise*1).ab.
14. RELAPSE PREVENTION/
15. "RELAPSE (Disorders)"/

16. or/10-15
[Controlled Trials Filter]
17. exp EXPERIMENTAL DESIGN/
18. TREATMENT EFFECTIVENESS EVALUATION/
19. MENTAL HEALTH PROGRAM EVALUATION/
20. (empirical study or longitudinal study or prospective study or quantitative study).md.
21. "2000".md. *[treatment outcome/clinical study]*
22. RETROSPECTIVE STUDIES/
23. EVIDENCE BASED PRACTICE/
24. (study or trial or treatment* or intervention or therap* or psychotherap*).ti.
25. (control* adj3 (group*1 or study or trial)).ti,ab,id.
26. (waitlist* or wait list* or treatment* as usual or TAU or care as usual or standard care or standard treatment*).ti,ab,id.
27. placebo.ti,ab,id.
28. PLACEBO/
29. (RCT or random*).ti,ab,id.
30. (crossover* or cross over*).ti,ab,id.
31. (quasi experimental).ti,ab,id.
32. (longitudinal or cohort).ti,ab,id.
33. (case adj (control or report or series)).ti,ab,id.
34. (cross-sectional).ti,ab,id.
35. (experimental or quantitative or pilot).ti,ab,id.
36. or/17-35
37. (9 and 16 and 36)
[Psychotherapies]
38. exp PSYCHOTHERAPY/
39. exp PSYCHOTHERAPEUTIC TECHNIQUES/
40. exp COGNITIVE TECHNIQUES/
41. exp COUNSELING/
42. 3300.cc. [Classification Code: Health & Mental Health Treatment & Prevention]
43. 3310.cc. [Classification Code: Psychotherapy & Psychotherapeutic Counseling]
44. 3311.cc. [Classification Code: Cognitive Therapies]
45. 3312.cc. [Classification Code: Behavior Therapy & Behavior Modification]
46. 3313.cc. [Classification Code: Group & Family Therapy]
47. 3314.cc. [Classification Code: Interpersonal & Client Centered & Humanistic Therapy]
48. 3315.cc. [Classification Code: Psychoanalytic Therapy]
49. (CBT or c-CBT or iCBT or coping skills or counsel?ing or mindfulness or psychoanal* or psychotherap* or rehabilitat*).ti,ab,id.
50. ((psychologic* or psychodynamic or behavio?r or cognitive) adj3 (intervent* or therap* or treat* or manag*)).ti,ab,id.
51. (Abreaction or Acting Out or Adlerian or Adolescent Psychotherap* or Age Regression or Analytical Psychotherap* or Anger Control or Anger Management or Art Therap* or Assertive* Training or Autogenic Training or Autosuggestion or Aversion Therap* or Balint Group or Behavio?r Contracting or Behavio?r Modification or Behavio?r Therap* or Bibliotherap* or Biofeedback or Body Psychotherap* or Brief Psychotherap* or Caregiver Support or Child Psychotherap* or Client Cent* Therapy or Cognitive Behavio?r Therap* or Cognitive Behavio?ral Stress Management or Cognitive Rehabilitation or Cognitive Restructuring or Cognitive Therap* or Colo?r Therap* or Conjoint Therap* or Contingency Management or Conversion Therap* or Conversational Therap* or Countertransference or Couples Therap* or Covert Sensitization or Crisis Intervention).ti,ab,id,de.
52. (Dance Therap* or Dialectical Behavio?r Therap* or (Dream* adj3 Analys*) or Eclectic

Psychotherap* or Eclectic Therap* or Emotion* Focus* Therap* or Emotional Freedom Technique or Encounter Group Therap* or Existential Therap* or Experiential Psychotherap* or Exposure Therap* or Expressive Psychotherap* or Eye Movement Desensiti#ation or Family Therap* or Free Association or Geriatric Psychotherap* or Gestalt Therap* or Griefwork or Group Psychotherap* or Group Therap* or Guided Image* or Holistic Psychotherap* or Humanistic Psychotherap* or Hypnosis or Hypnotherapy or Hypnoti#zability or Implosive Therap* or Individual Psychotherap* or Insight Therap* or Integrative Psychotherap* or Integrative Therap* or Interpersonal Psychotherap*).ti,ab,id,de.
53. (Logotherap* or Marathon Group Therap* or Marital Therap* or Meditation or Mental Healing or Metacognitive Therap* or Milieu Therap* or Mind train* or Morita Therap* or Music Therap* or Narrative Therap* or Nondirective Therap* or Personal Construct Therap* or Person Cent* Therap* or Persuasion Therap* or Pet Therap* or Play Therap* or Primal Therap* or Problem Solving Therap* or Psychoanalysis or Psychoanalytic Therap* or Psychodrama or Psychodynamic Psychotherapy or Psychotherapeutic Counsel* or Psychotherapeutic Processes or Psychotherapeutic Training or (Psychotherap* adj3 Rational-Emotive)) .ti,ab,id,de.
54. (Rational Emotive Behavio?r Therap* or Reality Therap* or Reciprocal Inhibition Therap* or Relationship Therap* or Relaxation Stress Management or Relaxation Technique* or Relaxation Therap* or Relaxation Training or Reminiscence Therap* or Role Playing or Self Analys* or Self Esteem Building or Sensitivity Training Group* or Sex Therap* or Sleep Phase Chronotherap* or Socioenvironmental Therap* or Sociotherap* or Solution Focused Therap* or Support Group* or (Support adj3 Psycho*) or Systematic Desensiti#ation or Therapeutic Communit* or Transactional Analysis or Validation Therap*).ti,ab,id,de.
55. or/38-54
[Antidepressants]
56. PSYCHOPHARMACOLOGY/ or NEUROPSYCHOPHARMACOLOGY/
57. 3340.cc. *[Classification Code: Clinical Psychopharmacology]*
58. exp ANTIDEPRESSANT DRUGS/
59. NEUROTRANSMITTER UPTAKE INHIBITORS/ or exp SEROTONIN NOREPINEPHERINE REUPTAKE INHIBITORS/ or exp SEROTONIN REUPTAKE INHIBITORS/
60. exp MONOAMINE OXIDASE INHIBITORS/
61. exp TRICYCLIC ANTIDEPRESSANT DRUGS/
62. (antidepress* or anti depress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic*).ti,ab,id,de.
63. (Agomelatine or Alnespirone or Amoxapine or Amfebutamone or Amiflamine or Amineptine or Amitriptylin* or Amitriptylinoxide or Amoxapine or (Atomoxetine or Tomoxetine) or Benactyzine or Brofaromine or Bupropion or Butriptylin* or Cianopramine or Cilobamine or Citalopram or (Chlorimipramin* or Clomipramin* or Chlomipramin* or Clorimipramine) or Clorgyline or Clovoxamine or (CX157 or Tyrima) or Dapoxetine or Deanol or Dibenzepin* or Demexiptilin* or Deprenyl or Desipramine or Desvenlafaxine or Dibenzepin or Dimetacrin* or (Dosulepin or Dothiepin) or Doxepin or Duloxetine or DVS-233 or Enilospirone or Eptapirone or Escitalopram or Etoperidone or Femoxetine or Fluotracen or Fluoxetine or Fluparoxan or Furazolidone or Fluvoxamine or Harmaline or Harmine or Hyperforin or Hypericum or John* Wort or Idazoxan or Imipramin* or Iprindole or Iproniazid* or Ipsapirone or Imipraminoxide or Isocarboxazid* or Lesopitron or Levomilnacipran or Lithium or Lofepramin* or (Lu AA21004 or Vortioxetine) or Lu AA24530 or LY2216684 or Maprotiline or Medifoxamine or Melitracen or Metapramine or

Mianserin or Milnacipran or Minaprine or Mirtazapine or Moclobemide or Nefazodone or Nialamide or Nitroxazepine or Nomifensine or Norfenfluramine or Nortriptyline or Noxiptilin* or Opipramol or Oxaflozane or Paroxetine or Phenelzine or Pheniprazine or Pipofezin* or Pirandamine or Piribedil or Pirlindole or Pivagabine or Pizotyline or Propizepine or (Protriptylin* or Pertofrane) or Quinupramine or Quipazine or Reboxetine or Ritanserin or Rolipram or Scopolamine or Selegiline or Sertraline or (Setiptiline or Teciptiline) or Tandospirone or Tetrindole or Thiazesim or Thozalinone or Tianeptin* or Toloxatone or Tranylcypromine or Trazodone or Trimipramine or 5-Hydroxytryptophan or 5-HT or Tryptophan or Hydroxytryptophan or Venlafaxine or Viloxazine or Vilazodone or Viqualine or Zalospirone or Zimeldine or (Alaproclate or Caroxazone or Diclofensine or Fenfluramine)) .ti,ab,id,de.
64. or/56-63
[Mood Stabilisers or Antipsychotics]
65. MOOD STABILIZERS/
66. exp ANTICONVULSIVE DRUGS/
67. exp NEUROLEPTIC DRUGS/
68. ((mood stabili?er*1 or lithium or eslicarbazepine or licarbazepine or valnoctamide or carbamazepine or valproate or valproic acid or divalpro* or ziprasidone or gabapentin or lamotrigine or topiramate) or (antipsychotic*1 or amisulpride or aripiprazole or asenapine or cariprazine or clozapine or haloperidol or iloperidone or lurasidone or olanzapine or quetiapin* or paliperidone or prosulpride or risperidone)).ti,ab,id,de.
69. or/65-68
70. (9 and (55 or 64 or 69) and 36)
71. 37 or 68 *(c3000 hits)*

B – Characteristics of included studies

Gelenberg 2003

Methods	Design: RCT Phases: acute (12 weeks), continuation (16 weeks), maintenance (52 weeks) Comparison groups: nefadozodone versus placebo Funded by: Bristol-Myers Squibb
Participants	Number of participants randomized (NRCT: number of participants included): 160 Criteria for relapse/recurrence: "If depressive symptoms began to emerge, as evidenced by a HAM-D-24 score of 16 or greater, another evaluation was scheduled within 2 weeks. Evaluations continued every 2 weeks until either the symptoms subsided or recurrence criteria were met. Recurrence was defined as a HAM-D-24 score of 16 or greater, together with a diagnosis of MDD as determined from a DSM-IV MDD checklist administered by the independent evaluator, on two consecutive visits. At the second of these visits, the recurrence also needed confirmation by each site's senior investigator based on a clinical interview. In addition, because some patients had elevated HAM-D-24 scores but did not meet MDD criteria, or discontinued before the confirmatory visit, a committee of senior investigators conducted a blinded review of all patient data at the end of the study. Recurrence was declared if there was consensus among the committee that an episode of MDD had occurred. The committee also indicated the date of onset of the recurrence. The final definition of time-to-recurrence was based on the first recurrence declared by either one of the two methods to define recurrence." (p. 809) Age distribution in sample M(SD): nefazodone: 44.4(11.1), placebo: 44.1(8.4) Sex distribution in sample (% female): nefazodone 69.7; placebo 65.5 Diagnoses in sample: nefazodone: 34.2% chronic major depressive disorder, 36.8% double depression, 29.0% recurrent depressive disorder without complete remission between episodes; placebo: 28.6% chronic major depressive disorder, 42.9% double depression, 28.6% recurrent depressive disorder without complete remission between episodes Depression severity at continuation/maintenance baseline M(SD): HAM-D-24 nefazodone: 5.9(4.4); placebo: 5.6(4.0) Mean age of onset M(SD): nefazodone: 24.1(13.3); placebo: 27.7(12.7) Length current/last major episode in months: nefazodone: 100.8(129.6);

	placebo: 87.6(90.0)
Interventions	Maintenance treatment (52 weeks) Nefazodone (N = 76) Name (class and type): nefazodone (SNDRI) Planned number of sessions or dosage of drug: 300 to600mg/day Number of sessions or dosage of drug M(SD): 485.9(115.6)mg/day Placebo (N = 84) Name (class and type): placebo Planned number of sessions or dosage of drug: / Number of sessions or dosage of drug M(SD): 504.0(115.9)mg/day Notes: For all medication visits, any formal psychotherapeutic interventions were proscribed. Participants in the placebo arm received identical (but inactive) tablets without any tapering down between continuation and maintenance phase.
Outcomes	1. Relapse/Recurrence 2. HAMD-24 mean 3. Dropout any 4. Dropout due to adverse events
Notes	Probably conflict of interest because of funding.

Harrison 1986

Methods	Design: RCT Phases: continuation treatment (26.1 weeks) after response to phenelzine treatment Comparison groups: phenelzine versus placebo Funded by: probably internal funding of the authors institution, no information given
Participants	Number of participants randomized (NRCT: number of participants included): 12 Criteria for relapse/recurrence: “Patients were considered to have relapsed and were withdrawn from the protocol if they scored 3 or more on the CGI for 2 consecutive weeks. Patients received a score of 3 on the CGI only if they had a clear recurrence of depressive symptoms.” (p. 347)

	Age distribution in sample M(SD): unclear Sex distribution in sample (% female): 83.3 Diagnoses in sample: phenelzine: 20.0% dysthymia, 80.0% double depression; placebo: 58.0% dysthymia, 42.0% double depression Depression severity at continuation/maintenance baseline M(SD): HAM-D phenelzine: 1.8(1.3); placebo: 4.4(3.9) Mean age of onset M(SD): unclear Length current/last major episode in months M(SD): unclear
Interventions	Continuation treatment (26.1 weeks) Phenelzine (N = 5) Name (class and type): phenelzine (MOI) Planned number of sessions or dosage of drug: unclear Number of sessions or dosage of drug M(SD): 51.0(7.4)mg/day Placebo (N = 7) Name (class and type): pill placebo Planned number of sessions or dosage of drug: / Number of sessions or dosage of drug M(SD): / Notes: The placebo group discontinued phenelzine treatment over a period of 14 days by tapering the daily dose by 15mg every 2 to 3 days according to a predetermined schedule. No information about concomitant treatments.
Outcomes	1. Relapse/Recurrence 2. HAM-D mean 3. Dropout any 4. Dropout due to adverse event 5. Experiencing any adverse event (no data available for the placebo group) 6. Serious adverse events (no data available for the placebo group)
Notes	After relapse, participants were treated openly as clinically indicated.

Hellerstein 2001

Methods	Design: RCT Phases: acute (8 weeks), continuation (16 weeks) Comparison groups: fluoxetine versus fluoxetine + group psychotherapy Funded by: this study was supported by a grant from the Eli Lilly Company.
Participants	Number of participants randomized (NRCT: number of participants included): 40 Criteria for relapse/recurrence: not available Age distribution in sample M(SD): 45.1(9.8) Sex distribution in sample (% female): 50.0 Diagnoses in sample: 100% dysthymia Depression severity at continuation/maintenance baseline M(SD): HAM-D 21 fluoxetine: 7.8(4.7); combination: 6.2(4.9) Mean age of onset M(SD): unclear Length current/last major episode in months M(SD): unclear
Interventions	Continuation treatment (16 weeks) Fluoxetine (N = 18) Name (class and type): fluoxetine (SSRI) Planned number of sessions or dosage of drug: 20 to 80mg/day Number of sessions or dosage of drug M(SD): 38.8(18.9) mg/day Combination (N = 19) Name (class and type): fluoxetine (SSRI) + group psychotherapy (CT/IPT) Planned number of sessions or dosage of drug: 20-80mg/day + 16 sessions Number of sessions or dosage of drug M(SD): 37.4(17.3) mg/day Notes: Participants were not allowed to currently undergo another psychotherapy. In the medication group, psychiatrists were instructed not to engage in psychotherapy, counseling, or supportive interventions.
Outcomes	1. HAM-D-21 mean (end of intervention and follow-up) 2. Dropout any 3. SWLS (end of intervention and follow-up)
Notes	Possibly conflict of interest (funded by Eli Lilly); discrepant information given in text vs. tables; sometimes also unclear/discrepant: information given in text itself; treatment/group therapy = CIGP-CD manual --> is not classified

	by Cochrane.

Keller 1998

Methods	Design: RCT Phases: acute (12 weeks), continuation (16 weeks), maintenance (76 weeks) Comparison groups: sertraline versus placebo Funded by: grant from Pfizer (NY)
Participants	Number of participants randomized (NRCT: number of participants included): 161 Criteria for relapse/recurrence: recurrence: DSM-III-R criteria for major depression for at least three weeks; CGI severity score of four or more (at least moderate severity); CGI improvement score of three or more (minimally improved or less); and an increase in HAM-D score of four or more points higher than the maintenance baseline; next visit one week later --> in total at least four weeks of clinical worsening; additionally: senior investigator supporting diagnosis/recurrence (p. 1666/1667) Age distribution in sample M(SD): sertraline: 40.8(9.0); placebo: 42.4(9.7) Sex distribution in sample (% female): sertraline: 62.3; placebo: 69.0 Diagnoses in sample: sertraline: 52.0% chronic major depressive disorder, 48.0% double depression; placebo: 43.0% chronic major depressive disorder, 57.0% double depression Depression severity at continuation/maintenance baseline M(SD): sertraline: 5.5(4.2); Placebo: 6.3(3.7) Mean age of onset M(SD): sertraline: 24.9(11.2); placebo: 25.7(12.5) Length current/last major episode in months M(SD): sertraline: 88.2(121.7) placebo: 54.9(80.8)
Interventions	Maintenance treatment (76 weeks) Sertraline (N = 77) Name (class and type): sertraline (SSRI) Planned number of sessions or dosage of drug: 50 to 200mg/day Number of sessions or dosage of drug M(SD): 146.1mg/day Placebo (N = 84) Name (class and type): placebo pills Planned number of sessions or dosage of drug: unclear Number of sessions or dosage of drug M(SD): 3.4 pills/day

	Notes: Participants in the placebo arm tapered sertraline by 50mg reduction per week as placebo substitution. No information about concomitant treatments.
Outcomes	1. Relapse/recurrence 2. HAM-D-24 mean 3. Dropout any 4. SF-36 5. Dropout due to adverse event 6. Experiencing any adverse event
Notes	Probably conflict of interest because of funding. They used 2 different criteria for relapse/recurrence, we extracted the stricter one --> therefore, maybe less relapse observed than actual happened, in combination with lots of dropouts --> bias of results? "Patients meeting recurrence criteria could continue in the study if both patient and study physician agreed that no change in the study medication was indicated at that time. Instead, an increase in daily dose was undertaken at a rate of 50mg/week up to the maximum daily dose of 200mg of sertraline hydrochloride. A similar double-blind titration was also used for patients receiving placebo treatment." (further details see p. 1667)

Klein 2004

Methods	Design: RCT Phases: acute (12 weeks), continuation (16 weeks), maintenance (52 weeks) Comparison groups: CBASP versus assessment only Funded by: Bristol-Myers Squibb
Participants	Number of participants randomized (NRCT: number of participants included): 82 Criteria for relapse/recurrence: "Recurrence was defined in the protocol as a HRSD-24 score of 16 or greater on two consecutive visits and a diagnosis of MDD as determined from a DSM–IV MDD checklist administered by the independent evaluator. At the second of these visits, the recurrence also needed confirmation by the site's senior investigator on the basis of a clinical interview" (p. 683) Age distribution in sample M(SD): CBASP: 44.2(11.7); assessment only: 46.0(11.1)

	Sex distribution in sample (% female): CBASP: 81.0; assessment only: 52.5 Diagnoses in sample: CBASP: 50.0% chronic major depressive disorder, 26.2% double depression, 23.8% recurrent depressive disorder with incomplete remission between episodes; assessment only: 60.0% chronic major depressive disorder, 20.0% double depression, 20.0% recurrent depressive disorder with incomplete remission between episodes Depression severity at continuation/maintenance baseline M(SD): HRSD-24 CBASP: 6.6(3.8); assessment only: 6.2(4.4) Mean age of onset M(SD): CBASP: 27.0(12.4); assessment only: 29.5(13.5) Length current/last major episode in months M(SD): CBASP: 92.4(115.2); assessment only: 85.2(122.4)
Interventions	Maintenance treatment (52 weeks) Name (class and type): CBASP Planned number of sessions or dosage of drug: 13 Number of sessions or dosage of drug M(SD): 11.1(3.8) Name (class and type): assessment only Planned number of sessions or dosage of drug: 13 Number of sessions or dosage of drug M(SD): unclear Notes: “In both conditions, all psychotropic medication and nonprotocol psychotherapy were prohibited.” (p. 683)
Outcomes	1. Relapse/recurrence 2. HRSD-24 mean 3. Dropout any
Notes	Probably conflict of interest because of funding.

Kocsis 1995

Methods	Design: NRCT Phases: acute (6 to10 weeks), continuation (16 to 20 weeks), maintenance (104,4 weeks) Comparison groups: imipramine versus desipramine Funded by: no information
Participants	Number of participants randomized (NRCT: number of participants included): 73 Criteria for relapse/recurrence: no information; this outcome was not

	addressed here. Age distribution in sample M(SD): 36.0(10.0) Sex distribution in sample (% female): 64.1 Diagnoses in sample: 37.0% dysthymia, 63.0% double depression Depression severity at continuation/maintenance baseline M(SD): unclear Mean age of onset M(SD): unclear Length current/last major episode in months M(SD): unclear
Interventions	Continuation treatment (16 to 20 weeks) Impipramine (N = 23) Name (class and type): imipramine (TCA) Planned number of sessions or dosage of drug: 300mg/day Number of sessions or dosage of drug M(SD): unclear Sertraline (N = 50) Name (class and type): desipramine (TCA) Planned number of sessions or dosage of drug: 200mg/day Number of sessions or dosage of drug M(SD): 232(72) mg/day Notes: “Patients were allowed to remain in stable long-term psychotherapy during the study but were not allowed to enter into new psychotherapy arrangements.” (p. 214) No data provided about the percentage of participants receiving parallel psychotherapy. “Concomitant psychotropic medications were proscribed.“ (p. 214)
Outcomes	1. Dropout any 2. Dropout due to adverse event
Notes	There were three different treatment arms in the acute treatment, but it is unclear how participants were allocated to the different treatment arms, for example if there were randomized. Additionally, the rationale of the acute treatment is unclear (for example some participants received medication on a double blind and some on an open basis).

Kocsis 1996

Methods	Design: RCT Phases: acute (10 weeks), continuation (16 weeks), maintenance (104.4 weeks) Comparison groups: desipramine versus placebo Funded by: grant from the National Institute of Mental Health
Participants	Number of participants randomized (NRCT: number of participants included): 53 Criteria for relapse/recurrence: "Suspected relapse occurred when a HAM-D score rose above 12 during the maintenance phase. Clinicians discussed and encouraged compliance and obtained a plasma drug level, which was reviewed by a nonblind observer who was not involved in the treatment. The nonblind observer gave instructions or dummy instructions for dosage adjustments. Relapse was defined as HAM-D scores greater than 12 and GAS scores below 60 on three successive ratings over a period of 4 weeks or at least one rating meeting these criteria and an urgent need for alternative treatment for a depressive syndrome." (p. 771) Age distribution in sample M(SD): 36.9(9.6) Sex distribution in sample (% female): 57.4 Diagnoses in sample: 10.9% chronic major depressive disorder, 39.5% dysthymia, 49.6% double depression Depression severity at continuation/maintenance baseline M(SD): unclear Mean age of onset M(SD): 12.6(6.9) Length current/last major episode in months M(SD): unclear
Interventions	Maintenance treatment (104.4 weeks) Desipramine (N = 28) Name (class and type): desipramine (TCA) Planned number of sessions or dosage of drug: 75 to 350mg/day Number of sessions or dosage of drug M(SD): unclear Placebo (N = 25) Name (class and type): placebo Planned number of sessions or dosage of drug: subjects in the placebo group were tapered by approximately 25% per week over the month and then received identical placebo at the same dose equivalent for the next 23 months or until relapse. Number of sessions or dosage of drug M(SD): unclear Notes: Participants in the placebo arm were tapered down by 25% per week

	during the first month of maintenance treatment followed by receiving identical placebo pills. Stable psychotherapeutic treatment was allowed during the study, 39% of participants from the desipramine group and 40% of participants from the placebo group were in stable psychotherapeutic treatment during the study.
Outcomes	1. Relapse/recurrence 2. Dropout any
Notes	Desipramine (norpramine) and matching placebo were provided by Marion Merrill Dow Inc., Kansas City, Mo.

Kocsis 2003

Methods	Design: NRCT Phases: acute (12 weeks), continuation (16 weeks), maintenance (52 weeks) Comparison groups: nefazodone versus CBASP versus combination Funded by: Bristol-Myers Squibb
Participants	Number of participants randomized (NRCT: number of participants included): 329 Criteria for relapse/recurrence: "Two definitions of relapse were utilized. Any patient who scored higher than 15 on the HAM-D was considered at risk for a relapse of MDD. In all such cases, an independent evaluator completed the DSM-IV criteria checklist for MDD, and if the patient met DSM-IV symptom criteria, the treating clinician was notified. A confirmatory visit was scheduled within 14 days and the HAM-D and MDD criteria checklist assessment were repeated. Patients meeting MDD criteria were evaluated by an independent senior investigator to confirm relapse. In addition, an investigator could declare a relapse on de facto grounds in the case of an exacerbation of depressive symptomatology with marked incapacity and clinically significant suicidal ideation, including psychiatric hospitalizations resulting from such exacerbations. Patients not meeting relapse criteria but continuing to score higher than 15 on the HAM-D were followed every other week until their outcome was clarified." (p. 77) Age distribution in sample M(SD): nefazodone: 43.1(9.7); CBASP: 44.0(10.8); combination: 44.6(9.4) Sex distribution in sample (% female): nefazodone: 58.7; CBASP: 66.3; combination: 67.8 Diagnoses in sample: nefazodone: 32.6% chronic major depressive disorder, 41.3% double depression, 26.1% recurrent depressive disorder with incomplete remission between episodes; CBASP: 33.7% chronic major depressive disorder, 46.1% double depression, 20.2% recurrent depressive

	disorder with incomplete remission between episodes; combination: 32.2% chronic major depressive disorder, 42.1% double depression, 26.6% recurrent depressive disorder with incomplete remission between episodes Depression severity at continuation/maintenance baseline M(SD): unclear Mean age of onset M(SD): nefazodone: 26.3(13.1); CBASP: 28.1(13.5); combination: 27.0(12.9) Length current/last major episode in months M(SD): nefazodone: 92.4(114.0); CBASP: 105.6(144.0); combination: 99.6(120.0)
Interventions	Continuation treatment (16 weeks) Nefazodone (N = 91) Name (class and type): nefazodone (SNDRI) Planned number of sessions or dosage of drug: 300-600mg/day Number of sessions or dosage of drug M(SD): 499(115)mg/day CBASP (N = 88) Name (class and type): CBASP Planned number of sessions or dosage of drug: 6 sessions Number of sessions or dosage of drug M(SD): 6(1) sessions Combination (N = 150) Name (class and type): combination (SNDRI+CBASP) Planned number of sessions or dosage of drug: 300-600mg/day + 6 sessions Number of sessions or dosage of drug M(SD): 479(108)mg/day + 5.9(1.1) sessions Notes: “Pharmacotherapists were directed not to provide any psychotherapeutic interventions.” (p. 76)
Outcomes	1. Relapse/recurrence 2. Dropout any
Notes	Probably conflict of interest because of funding and conncection of the authors to pharmaceutical industry.

Koran 2001

Methods	Design: NRCT Phases: acute (12 weeks), continuation (16 weeks), maintenance (76 weeks) Comparison groups: sertraline versus imipramine Funded by: grant from Pfizer (NY)
Participants	Number of participants randomized (NRCT: number of participants included): 386 Criteria for relapse/recurrence: "A full remission of depression was defined as a CGI improvement score (CGI-I) (Guy, 1976) of 1 or 2 (very much or much improved) and a Hamilton Depression Rating Scale score (HRSD) (Hamilton, 1960) ≤ 7. A satisfactory therapeutic response (partial remission) was defined as a CGI-I ≥2, a HRSD ≤ 15 with a ≥ 50% decrease from baseline, and a CGI severity score (CGI-S) ≤ 3 (i.e. no more than mild depression). A patient whose scores dropped below a 'satisfactory therapeutic response' for a 4-week period was considered relapsed." (p. 29) Age distribution in sample M(SD): sertraline: 40.2(9.7); imipramine: 43.1(9.6) Sex distribution in sample (% female): sertraline: 68.2; imipramine: 57.1 Diagnoses in sample: sertraline: 49.0% chronic major depressive disorder, 51.0% double depression; imipramine: 45.0% chronic major depressive disorder, 55.0% double depression Depression severity at continuation/maintenance baseline M(SD): sertraline: 6.7(3.7); impramine: 6.9(3.5) Mean age of onset M(SD): unclear Length current/last major episode in months M(SD): sertraline: 73.2(98.4); imipramine: 76.8(114.0)
Interventions	Continuation treatment (16 weeks) Sertraline (N = 239) Name (class and type): sertraline (SSRI) Planned number of sessions or dosage of drug: 50 to 200mg/day Number of sessions or dosage of drug: 149(55)mg/day Imipramine (N = 147) Name (class and type): imipramine (TCA) Planned number of sessions or dosage of drug: 50 to 300mg/day Number of sessions or dosage of drug: 227(73)mg/day Notes: "Psychotherapy was not allowed during the study unless it had started at least 3 months before acute phase randomization and continued throughout

	all stages of the study without change." (p. 28) 60% of the participants received ongoing psychotherapy during the continuation phase.
Outcomes	1. Relapse/recurrence 2. HAM-D-24 mean 3. Dropout any 4. Q-LES-Q score 5. Dropout due to adverse event
Notes	Probably conflict of interest because of funding (authors = members of industry who financed study). Further randomized comparison on maintenance treatment of the sertraline group with placebo in the publication of Keller (1998).

Miller 2001

Methods	Design: RCT Phases: acute (10 to 12 weeks), continuation (16 weeks), maintenance (104.4 weeks) Comparison groups: desipramine versus placebo Funded by: Supported by grant R01-MH37103 from the National Institute of Mental Health and from a fund established in the New York Community Trust by DeWitt-Wallace.
Participants	Number of participants randomized (NRCT: number of participants included): 27 Criteria for relapse/recurrence: "Recurrence was defined as HAM-D scores > 12 and GAS scores < 60 on three successive ratings over a period of 4 weeks or at least one rating meeting theses criteria and an urgent need for alternative treatment for recurrence of depressive symptoms." (p. 233) Age distribution in sample M(SD): desipramine: 34.4(9.6), placebo: 39.0(11.2) Sex distribution in sample (% female): desipramine: 43.0, placebo: 46.0 Diagnoses in sample: 100% dysthymia Depression severity at continuation/maintenance baseline M(SD): desipramine: 3.1(2.5), placebo: 3.9(5.2) Mean age of onset M(SD): desipramine: 14.5(10.4), placebo: 12.3(8.0) Length current/last major episode in months M(SD): unclear

Interventions	Maintenance treatment (104.4 weeks) Desipramine (N = 14) Name (class and type): desipramine (TCA) Planned number of sessions or dosage of drug: unclear Number of sessions or dosage of drug M(SD): 223(90)mg/day Placebo (N = 13) Name (class and type): placebo Planned number of sessions or dosage of drug: unclear Number of sessions or dosage of drug M(SD): 240(60)mg/day (dummy dosage) Notes: Participants in the placebo arm were tapered down by 25% per week during the first month of maintenance treatment followed by receiving identical placebo pills. 43% of participants from the DMI group and 38% of participants from the placebo group were in stable long-term psychotherapy during the study, a nonsignificant difference.
Outcomes	1. Relapse/recurrence
Notes	Analysis of the dysthymic subgroup of Kocsis et al 1996 and some additional dysthymic subjects.

C – Rating sheet of the KERI-D (English)

Coding system to assess interventions of relapse prevention in depression

Date _____ **Name of rater** _____

Mark/number of the video _____ **Therapy session**_____

Quality of sound:	**Disagree**	**Neither agree nor disagree**	**Strongly agree**
The therapist could be heard clearly	☐	☐	☐
The patient could be heard clearly	☐	☐	☐

(Further) notes:

A. Self-care	**Not at all**	**A little**	**Moderately**	**Considerably**	**Thoroughly**
1. Aspects of self-care					
a. Individual **self-care activities** are discussed	☐	☐	☐	☐	☐
b. Individual **patient resources** are discussed	☐	☐	☐	☐	☐
2. Implementation of self-care					
a. Specific **opportunities and resources** for practicing self-care are discussed	☐	☐	☐	☐	☐
b. Specific **difficulties** in practicing and maintaining self-care are discussed	☐	☐	☐	☐	☐
c. Specific **options for monitoring/evaluating** self-care are discussed	☐	☐	☐	☐	☐

B. Early warning signs	**Not at all**	**A little**	**Moderately**	**Considerably**	**Thoroughly**
1. Aspects of early warning signs					
a. Individual **early warning signs** (Cognition, Emotion, Somatization, Behavior) are discussed	☐	☐	☐	☐	☐
2. Dealing with early warning signs					
a. Specific **methods** to monitor and recognize early warning signs are discussed	☐	☐	☐	☐	☐
b. Specific **strategies** for dealing with early warning signs are discussed	☐	☐	☐	☐	☐
c. Specific **difficulties** in implementing the strategies are discussed	☐	☐	☐	☐	☐

C. Triggering events and situations

	Not at all	A little	Moderately	Considerably	Thoroughly
1. Aspects of triggering events and situations					
a. Individual **triggering events and situations** are discussed	☐	☐	☐	☐	☐
2. Dealing with triggering events and situations					
a. Specific **strategies to prepare** for triggering events and situations are discussed	☐	☐	☐	☐	☐
b. Specific **difficulties** in implementing the strategies are discussed	☐	☐	☐	☐	☐
c. Individual **symptoms of a relapse** and/or **an emergency kit/plan** for reacting to a relapse are discussed	☐	☐	☐	☐	☐

D. Termination of therapy and planning next steps

1. Aspects of termination of therapy					
a. The patient's most important **findings during therapy** and/or **achievements** are discussed	☐	☐	☐	☐	☐
b. The patient's personal **life goals** are discussed	☐	☐	☐	☐	☐
c. The patient's **emotions** and **cognitions** on terminating therapy are discussed	☐	☐	☐	☐	☐
2. Dealing with the termination of therapy					
a. **Options for contacting the therapist** after terminating therapy are discussed	☐	☐	☐	☐	☐
b. Concrete options for **continuing treatment** are discussed	☐	☐	☐	☐	☐
3. Importance of dealing with potential relapse(s)					
a. The **chance of a relapse** and/or the **significance of relapse prevention** are discussed	☐	☐	☐	☐	☐

→ Overall impression of the whole session: Transfer

From the therapist: The extent to which the therapist discusses (category A to D) topics in such a way that the patient is encouraged to implement and sustain skills, knowledge or competences gained in therapy into their daily routine and in the long run.	☐	☐	☐	☐	☐

D – Rating sheet of the KERI-D (German)

Kodierbogen zur **E**rfassung **R**ückfallprophylaktischer **I**nterventionen bei **D**epression **– KERI-D**

Datum _____ **Name des Raters_____**

Kennzeichen des Videos _____ **Therapiesitzung_____**

Tonqualität:	**Trifft nicht zu**	**Trifft mittel-mässig zu**	**Trifft sehr zu**
Der Therapeut war akustisch gut zu verstehen	☐	☐	☐
Der Patient war akustisch gut zu verstehen	☐	☐	☐

Weitere Anmerkungen:

A. Selbstfürsorge	**Trifft nicht zu**	**Trifft wenig zu**	**Trifft mittel-mässig zu**	**Trifft ziemlich zu**	**Trifft sehr zu**
3. Aspekte von Selbstfürsorge					
c. Es werden individuelle **Aktivitäten zur Selbstfürsorge** intensiv thematisiert.	☐	☐	☐	☐	☐
d. Es werden individuelle **Ressourcen** des Patienten intensiv thematisiert.	☐	☐	☐	☐	☐
4. Durchführung von Selbstfürsorge					
d. Es werden konkrete **Rahmenbedingungen oder Hilfsmittel** zur Durchführung der Selbstfürsorge intensiv thematisiert.	☐	☐	☐	☐	☐
e. Es werden konkrete **Schwierigkeiten** bei der Durchführung und Aufrechterhaltung der Selbstfürsorge intensiv thematisiert.	☐	☐	☐	☐	☐
f. Es werden konkrete **Möglichkeiten der Evaluation** von Selbstfürsorge intensiv thematisiert.	☐	☐	☐	☐	☐

B. Frühwarnsignale	**Trifft nicht zu**	**Trifft wenig zu**	**Trifft mittel-mässig zu**	**Trifft ziemlich zu**	**Trifft sehr zu**
3. Aspekte der Frühwarnsignale					
b. Es werden individuelle **Frühwarnsignale** (Kog., Emo., Som., Ver.) intensiv thematisiert.	☐	☐	☐	☐	☐
4. Umgang mit Frühwarnsignalen					
d. Es werden konkrete **Methoden** intensiv thematisiert, wie Frühwarnsignale beobachtet und erkannt werden können.	☐	☐	☐	☐	☐
e. Es werden konkrete **Strategien** zum Umgang mit Frühwarnsignalen intensiv thematisiert.	☐	☐	☐	☐	☐
f. Es werden konkrete **Schwierigkeiten** bei der Anwendung der Strategien intensiv thematisiert.	☐	☐	☐	☐	☐

C. Depressionsauslösende Ereignisse und Situationen

	Trifft nicht zu	Trifft wenig zu	Trifft mittel-mässig zu	Trifft ziemlich zu	Trifft sehr zu
3. Aspekte depressionsauslösender Ereignisse und Situationen					
b. Es werden individuelle **depressionsauslösende Ereignisse und Situationen** intensiv thematisiert.	☐	☐	☐	☐	☐
4. Umgang mit depressionsauslösenden Ereignissen und Situationen					
d. Es werden konkrete **Strategien zur Vorbereitung** auf depressionsauslösende Ereignisse und Situationen intensiv thematisiert.	☐	☐	☐	☐	☐
e. Es werden konkrete **Schwierigkeiten** bei der Anwendung der Strategien intensiv thematisiert.	☐	☐	☐	☐	☐
f. Es werden individuelle **Merkmale eines Rückfalls** und / oder der **Notfallplan,** als Hilfsmittel zur Reaktion auf einen Rückfall, intensiv thematisiert.	☐	☐	☐	☐	☐

D. Therapieabschluss und Zukunftsperspektive

	Trifft nicht zu	Trifft wenig zu	Trifft mittel-mässig zu	Trifft ziemlich zu	Trifft sehr zu
4. Aspekte des Therapieabschlusses					
d. Die wichtigsten persönlichen **Erkenntnisse der Therapie** und / oder **Erfolge des Patienten** werden intensiv thematisiert.	☐	☐	☐	☐	☐
e. Persönliche **Lebensziele** des Patienten werden intensiv thematisiert.	☐	☐	☐	☐	☐
f. Mit dem Therapieabschluss verbundene **Emotionen** oder **Kognitionen** des Patienten werden intensiv thematisiert.	☐	☐	☐	☐	☐
5. Umgang mit Therapieabschluss					
c. Die **Möglichkeit des Kontaktes** zum **Therapeuten** nach Therapieende wird konkret thematisiert.	☐	☐	☐	☐	☐
d. Es werden konkrete **weiterführende Angebote** intensiv thematisiert.	☐	☐	☐	☐	☐
6. Relevanz der Auseinandersetzung mit der Zukunft					
b. Die **Möglichkeit eines Rückfalls** und / oder die **Bedeutsamkeit der Rückfallprophylaxe** wird intensiv thematisiert.	☐	☐	☐	☐	☐

→ Gesamteindruck: Transfer & Langfristigkeit

Therapeutenangebot: Der Therapeut bearbeitet die Inhalte der Therapiesitzung in einer Weise, dass ein Transfer von der Therapie in den Alltag des Patienten nach Therapieende ermöglicht wird und gleichzeitig auch auf eine langfristige Wirkung abgezielt wird.	☐	☐	☐	☐	☐

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Curriculum vitae

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Academic education and employment

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Since 2015	Postgraduate education in cognitive behavior therapy and behavioral medicine at the University of Zurich, Switzerland (Master of Advanced Studies in Psychotherapy)
2013	Project collaborator at the Thurgau University of Teacher Education, Switzerland
2010-2012	MSc Psychology in Clinical Psychology and Health Psychology at the University of Zurich, Switzerland
2007-2010	BSc Psychology at the University of Leipzig, Germany

Teaching

2013-2016	Seminar on chronification of mental disorders (BSc)
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